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IMPROVED METHODS FOR THE PREPARATION OF GLYCALS

BY

ALLAN E. EARL ©

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE
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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled,

IMPROVED METHODS FOR THE PREPARATION OF GLYCALS

submitted by Allan E. Earl, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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Much appreciation is due to the members of the staff of the Department of Chemistry and the moral support of many fellow workers will not soon be forgotten.

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Finally, the author gratefully acknowledges the invaluable guidance provided by Professor R. U. Lemieux during the course of this work.

ABSTRACT

The classical preparation of acetylated 1,2-dideoxy-glyc-1-enopyranoses (acetylated glycals), the zinc dust reduction of acetylated glycosyl bromides, is known to be subject to highly variable yields owing to hydrolytic side-reactions. Magnesium amalgam was found to reduce acetylated glycopyranosyl bromides in N,N-dimethylformamide to acetylated glycals rapidly and in excellent yield. The method, which seems to be of general utility, was applied to seven configurations of starting materials in the pentose, hexose and disaccharide fields.

An investigation of the chemical properties of tri-O-acetyl-α-D-glucopyranose 1,2-(2'-hydroxyethyl orthoacetate) showed that this compound, in the presence of ethylene glycol and p-toluenesulfonic acid, readily underwent transorthoesterification to provide 3,4,6-tri-O-acetyl-D-glucopyranose. Such transformations were carried out with the corresponding derivatives of D-mannose and maltose.

The availability of the partially acetylated sugars, with the 1 and 2 hydroxyl groupings free, allowed the preparations of the 1,2-di-O-p-toluenesulfonate derivatives which were in turn converted to acetylated glycals by treatment with sodium iodide

in N,N-dimethylformamide.

The partially acetylated "1,2 diols" could be degraded to lower aldoses by periodate or lead tetraacetate oxidation. Thus, for example, maltose was degraded to 3-(α-D-glucopyranosyl)-D-arabinose.

TABLE OF CONTENTS

Page

ACKNOWLEDGEMENTS iii

ABSTRACT iv

LIST OF TABLES xi

LIST OF FIGURES .xiii

INTRODUCTION 1

EXPERIMENTAL 43

I. METHODS

1. Chromatography 43
   (a) Paper chromatography 43
   (b) Thin layer chromatography 43
   (c) Column chromatography 44
   (d) Counter-current distribution 44
2. Optical Rotations 45
3. Melting Points 45
4. Spectroscopic Data 45
   (a) Proton magnetic resonance 45
   (b) Infrared spectroscopy 45

II REAGENTS

1. Solvents 45
2. Non-carbohydrate reagents 46
3. Carbohydrate reagents 47

III. SYNTHETIC INVESTIGATION

1. Glycal synthesis by metallic reduction 54
    - (a) Tri-O-acetyl-1,2-dideoxy-D-*arabino*-hex-1-enopyranose (I)
        - (i) From tetra-O-acetyl-α-D-glucopyranosyl bromide (II) 54
        - (ii) From tetra-O-acetyl-α-D-mannopyranosyl bromide (III). . . 57
    - (b) Tri-O-acetyl-1,2-dideoxy-D-*lyxo*-hex-1-enopyranose (IV) 57
    - (c) Tri-O-acetyl-1,2-dideoxy-D-*ribo*-hex-1-enopyranose (VI)
        - (i) Tetra-O-acetyl-α-D-altropyranosyl bromide (XXVII) 58
        - (ii) Tri-O-acetyl-1,2-dideoxy-D-*ribo*-hex-1-enopyranose (VI). . . 59
    - (d) Tri-O-acetyl-1,2-dideoxy-D-*xylo*-hex-1-enopyranose (V) 59
    - (e) Di-O-acetyl-1,2-dideoxy-L-*erythro*-pent-1-enopyranose (XXVIII) 60
    - (f) 1,2-dideoxy-4-O-(α-D-glucopyranosyl)-D-*arabino*-hex-1-enopyranose (XXIX) . . 60
    - (g) 3,6-Di-O-acetyl-1,2-dideoxy-4-O-(tetra-O-acetyl-α-D-glucopyranosyl)-D-*arabino*-hex-1-enopyranose (XV). 61

2. Synthesis of tri-O-acetyl-D-glucal via tri-O-acetyl-1,2-di-O-*p*-toluenesulfonyl-α-D-glucopyranose (XXXIV)
    - (a) Tri-O-acetyl-1,2-O-(1-*exo*-2'-hydroxyethoxyethylidene)-α-D-glucopyranose
        - (i) From tetra-O-acetyl-α-D-glucopyranosyl bromide (II) 62
        - (ii) From tri-O-acetyl-1,2-O-(1-*exo*-ethoxyethylidene)-α-D-glucopyranose (XVI) 64
    - (b) 3,4,6-Tri-O-acetyl-α-D-glucopyranose (XXXII)
        - (i) From tri-O-acetyl-1,2-O-(1-*exo*-ethoxyethylidene)-α-D-glucopyranose (XVI) 66
        - (ii) From tetra-O-acetyl-α-D-pyranosyl bromide (II) 67
        - (iii) From 3,4,6-tri-O-acetyl-β-D-glucopyranosyl chloride (XXIII) . 69
        - (iv) Analytical periodate oxidation . . 69
        - (v) Preparative periodate oxidation . . 71
    - (c) 3,4,6-Tri-O-acetyl-2-O-*p*-toluenesulfonyl-α-D-glucopyranosyl chloride (XXXIII) 72
    - (d) Tri-O-acetyl-1,2-di-O-*p*-toluenesulfonyl-

α-D-glucopyranose (XXXIV) 73

(e) Tri-O-acetyl-1,2-dideoxy-D-arabino-hex-1-enopyranose (I) 74

3. Synthesis of tri-O-acetyl-D-glucal via tri-O-acetyl-1,2-di-O-p-toluenesulfonyl-α-D-mannopyranose (XXXV)

(a) 3,4,6-Tri-O-acetyl-D-mannopyranose (XVIII)

(i) From tri-O-acetyl-1,2-O-(1-exo-methoxyethylidene)-β-D-mannopyranose (XVII) 75

(ii) Analytical periodate oxidation . . 76

(iii) Preparative periodate oxidation . 77

(b) Tri-O-acetyl-1,2-di-O-p-toluenesulfonyl-α-D-mannopyranose (XXXV) 78

(c) Tri-O-acetyl-1,2-dideoxy-D-arabino-hex-1-enopyranose (I) 79

4. Synthesis of maltal via the acetylated 1,2-di-O-p-toluenesulfonyl compound

(a) 3,6-Di-O-acetyl-4-O-(tetra-O-acetyl-α-D-glucopyranosyl)-1,2-O-(1-exo-2'-hydroxyethoxyethylidene)-α-D-glucopyranose (XXXVI) 80

(b) 3,6,2',3',4',6'-Hexa-O-acetylmaltose (XXXVIII)

(i) From hepta-O-acetyl-α-maltosyl bromide (XXII) 82

(ii) Analytical periodate oxidation . . 84

(iii) Preparative periodate oxidation . 86

(c) 2,3,6,2',3',4',6'-Hepta-O-acetyl-β-maltose (XXXIX) 87

(d) Hexa-)-acetyl-1,2-di-O-p-toluenesulfonyl-α-maltose (XL) 87

(e) 1,2-Dideoxy-4-O-(α-D-glucopyranosyl)-D-arabino-hex-1-enopyranose (XXIX) . . . 88

DISCUSSION 91

BIBLIOGRAPHY 168

LIST OF TABLES

Page

TABLE I Oxidation of 3,4,6-tri-O-acetyl-α-D-glucopyrananose (XXXII) with periodate 71

TABLE II Oxidation of 3,4,6-tri-O-acetyl-D-mannopyranose (XVIII) with periodate 77

TABLE III Oxidation of 3,6,2',3',4',6'-hexa-O-acetylmaltose (XXXVIII) with periodate 85

TABLE IV N.m.r. parameters for tetra-O-acetyl-α-D-altropyranosyl bromide (XXVII) 99

TABLE V N.m.r. parameters for the tri-O-acetylated glycals in the hexapyranose series 106

TABLE VI N.m.r. parameters for the di-O-acetylated glycals in the pentopyranose series 109

Page

TABLE VII N.m.r. parameters for 1,2-dideoxy-4-O-(α-D-glucopyranosyl)-D-*arabino*-hex-1-enopyranose (XXIX) 112

TABLE VIII A comparison of the n.m.r. parameters of tri-O-acetyl-1,2-O-(1-*exo*-2'-hydroxyethoxyethylidene)-α-D-glucopyranose (XXX) with those of tri-O-acetyl-1,2-O-(1-*exo*-ethoxyethylidene)-α-D-glucopyranose (XVI) 134

TABLE IX N.m.r. parameters of tri-O-acetyl-α-D-glucopyranose (XXXII) 138

TABLE X N.m.r. parameters of tri-O-acetyl-2-O-*p*-toluenesulfonyl-α-D-glucopyranosyl chloride (XXXIII) 142

TABLE XI N.m.r. parameters of tri-O-acetyl-1,2-di-O-*p*-toluenesulfonyl-α-D-glucopyranose (XXXIV) 148

LIST OF FIGURES

Page

FIG. 1 N.m.r. spectrum (60 MHz) of tetra-O-acetyl-α-D-mannopyranosyl bromide (III) (deuteriochloroform) 49

FIG. 2 N.m.r. spectrum (60 MHz) of tetra-O-acetyl-α-D-galactopyranosyl bromide (XIX) (deuteriochloroform) 49

FIG. 3 N.m.r. spcetrum (60 MHz) of tri-O-acetyl-β-L-arabinopyranosyl bromide (XXI) (deuteriochloroform) 51

FIG. 4 N.m.r. spectrum (60 MHz) of tri-O-acetyl-1,2-O-(1-*exo*-ethoxyethylidene)-α-D-glucopyranose (XVI) (deuteriochloroform) 51

FIG. 5 N.m.r. spectrum (60 MHz) of tri-O-acetyl-1,2-O-(1-*exo*-methoxyethylidene)-β-D-mannopyranose (XVII) (deuteriochloroform) 53

FIG. 6 N.m.r. spectrum (100 MHz) of 2-hydroxyethyl tetra-O-acetyl-β-D-glucopyranose (XXIV) (deuteriochloroform) 53

Page

FIG. 7 N.m.r. spectrum (100 MHz) of 2-acetoxyethyl tetra-O-acetyl-α-D-glucopyranose (XXVI) (deuteriochloroform) 55

FIG. 8 N.m.r. spectrum (60 MHz) of tri-O-acetyl-1,2-dideoxy-D-arabino-hex-1-enopyranose (I) (deuteriochloroform) . 55

FIG. 9 N.m.r. spectrum (60 MHz) of tri-O-acetyl-1,2-dideoxy-D-lyxo-hex-1-enopyranose (IV) (deuteriochloroform) . . 97

FIG. 10 N.m.r. spectrum (100 MHz) of tetra-O-acetyl-α-D-altropyranosyl bromide (XXVII) (deuteriochloroform) 97

FIG. 11 N.m.r. spectrum (100 MHz) of tri-O-acetyl-1,2-dideoxy-D-ribo-hex-1-enopyranose (VI) (deuteriochloroform) . . 104

FIG. 12 N.m.r. spectrum (100 MHz) of di-O-acetyl-1,2-dideoxy-L-erythro-pent-1-enopyranose (XXVIII) (deuteriochloroform) 104

Page

FIG. 13 N.m.r. spectrum (100 MHz) of 1,2-dideoxy-4-O-(α-D-glucopyranosyl)-D-*arabino*-hex-1-enopyranose (XXIX) (deuterium oxide) 115

FIG. 14 N.m.r. spectrum (60 MHz) of tri-O-acetyl-1,2-O-(1-*exo*-2'-hydroxyethoxyethylidene)-α-D-glucopyranose (XXX) (deuteriochloroform) 115

FIG. 15 N.m.r. spectrum (60 MHz) of 3,4,6-tri-O-acetyl-α-D-glucopyranose (XXXII) (deuteriopyridine) 136

FIG. 16 Plot of sodium periodate oxidation of 3,4,6-tri-O-acetyl-α-D-glucopyranose (XXXII) 136

FIG. 17 N.m.r. spectrum (60 MHz) of 3,4,6-tri-O-acetyl-2-O-*p*-toluenesulfonyl-α-D-glucopyranosyl chloride (XXXIII) (deuteriochloroform) 144

FIG. 18 N.m.r. spectrum (60 MHz) of tri-O-acetyl-1,2-di-O-*p*-toluenesulfonyl-α-D-glucopyranose (XXXIV) (deuteriochloroform) 144

Page

FIG. 19 Plot of sodium periodate oxidation of 3,4,6-tri-O-acetyl-D-mannopyranose (XVIII) 156

FIG. 20 N.m.r. spectrum (60 MHz) of 3,6-di-O-acetyl-4-O-(tetra-O-acetyl-α-D-glucopyranosyl)-1,2-O-(1-exo-2'-hydroxyethoxyethylidene)-α-D-glucopyranose (XXXVI) (deuteriochloroform) 156

FIG. 21 N.m.r. spectrum (100 MHz) of 3,6,2',3',4',6'-hexa-O-acetylmaltose (XXXVIII) (deuteriochloroform) 161

FIG. 22 Plot of sodium periodate oxidation of 3,6,2',3',4',6'-hexa-O-acetylmaltose (XXXVIII) 161

FIG. 23 N.m.r. spectrum (100 MHz) of 2,3,6,2',3',4',6'-hepta-O-acetyl-β-maltose (XXXIX) (deuteriochloroform) 164

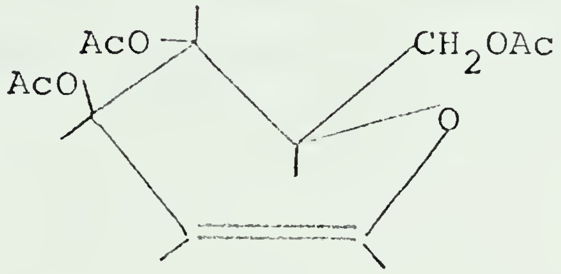
FIG. 24 N.m.r. spectrum (60 MHz) of tetra-O-acetyl-α-D-gulopyranosyl bromide (XLI) (deuteriochloroform) 164

Page

FIG. 25 N.m.r. spectrum (100 MHz) of tri-O-acetyl-1,2-dideoxy-D-*xylo*-hex-1-enopyranose (V) (deuteriochloroform) 167

INTRODUCTION

Carbohydrate compounds containing unsaturation between C1 and C2 have been well known since Fischer's synthesis (1) of tri-O-acetyl-D-glucal (I) in 1913.

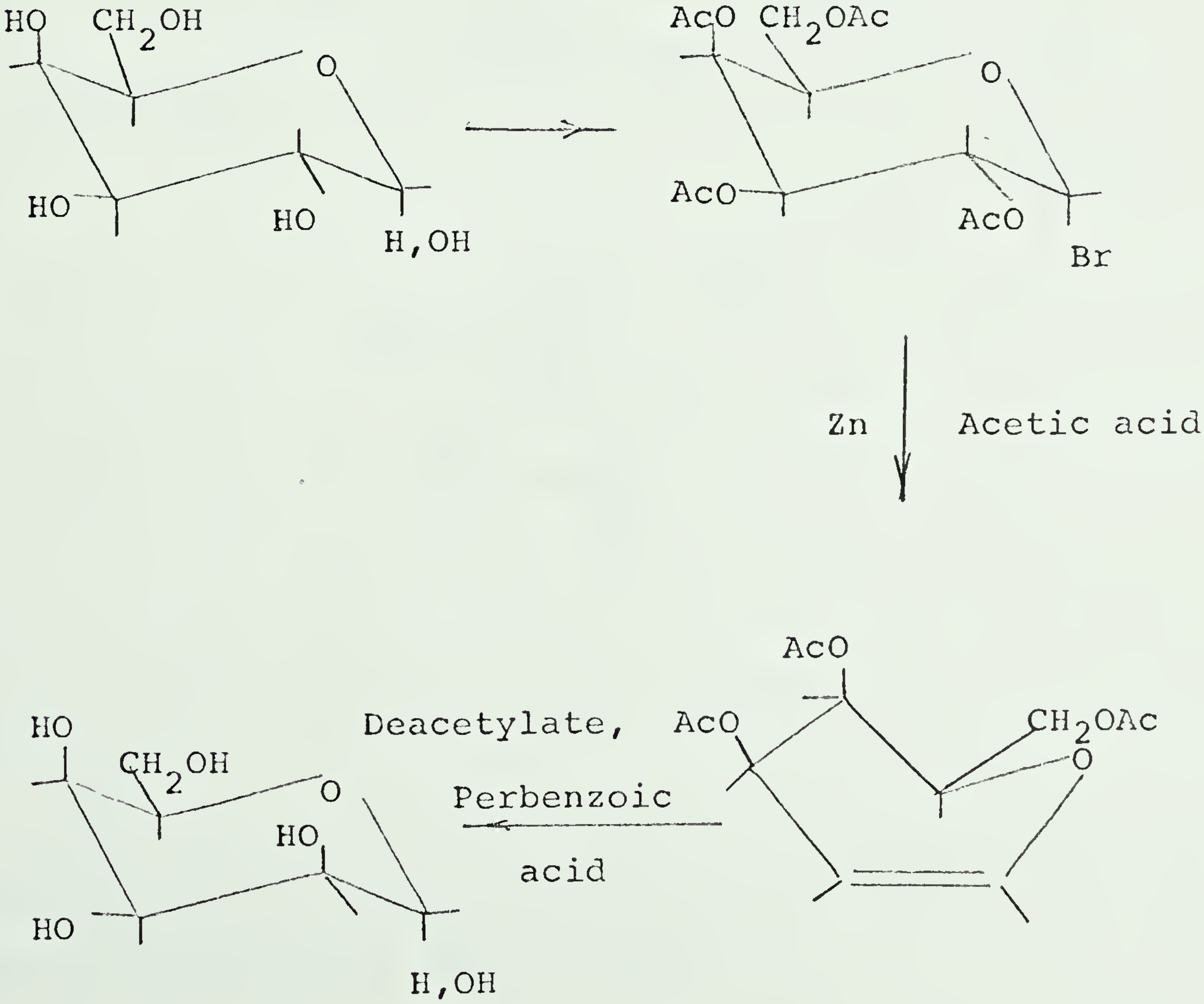


I

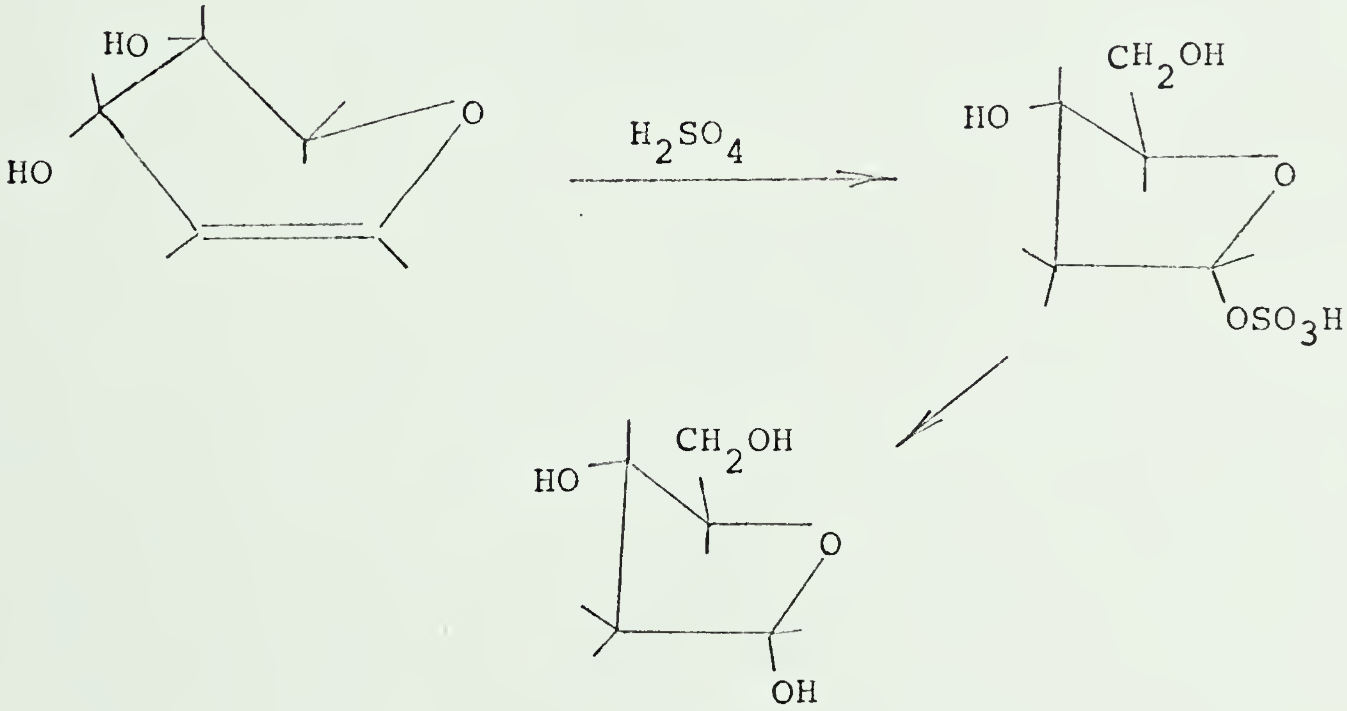
The rather unusual common name for this compound arose because the impure initial product acted as an aldehyde in test reactions. Unfortunately, this misnomer was carried over into the whole class of such compounds and they became known as acetylated glycals. These names remain today but are being superceded gradually by the modern terminology which labels compound I as tri-O-acetyl-1,2-dideoxy-D-arabino-hex-1-enopyranose.

The inital synthetic usefulness of these compounds was based on the fact that, in their preparation, the asymmetry of C2 of the carbohydrate chain was destroyed.

Thus the reverse procedure, that is, hydroxylation of a glycal, for example, using peracids (2) or osmium tetroxide (3) allowed, in many cases, the preparation of the epimeric sugars. This latter procedure made available many of the so-called rare sugars since reaction conditions could be worked out which maximized the yield of the desired product. Thus, Levene and Tipson (2) were able to convert D-galactose to its C2-epimer talose.

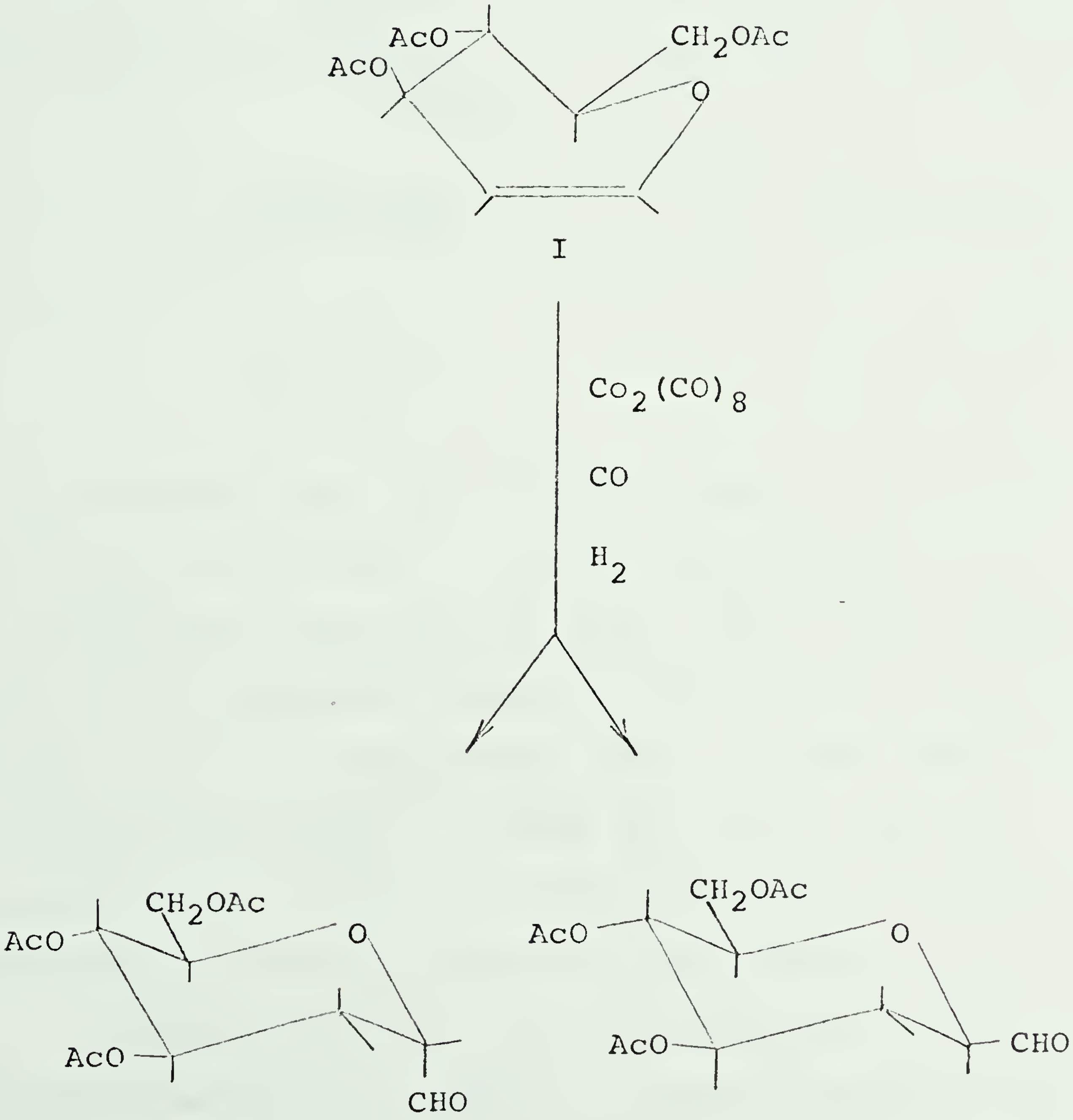

HO
CH2OH
O
HO
HO
H,OH
AcO
CH2OAc
O
AcO
AcO
Br
Zn
Acetic acid
AcO
Deacetylate,
AcO
CH2OAc
O
Perbenzoic
acid
HO
CH2OH
O
HO
HO
H,OH

Hydration of the double bond of glycals has formed the basis of the synthesis of another important group of compounds, the 2-deoxyaldoses (4). For example, the treatment of D-arabinal with sulfuric acid at low temperature followed by neutralization has led to the isolation of 2-deoxy-D-ribose.

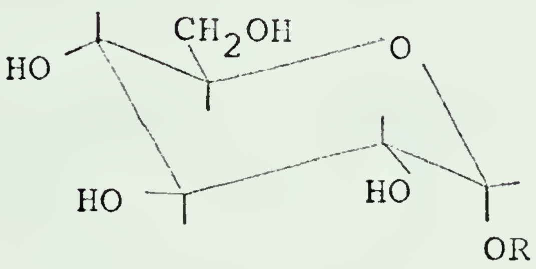


A commercial process for the preparation of 2-deoxy-D-glucose has been elaborated on a similar basis.

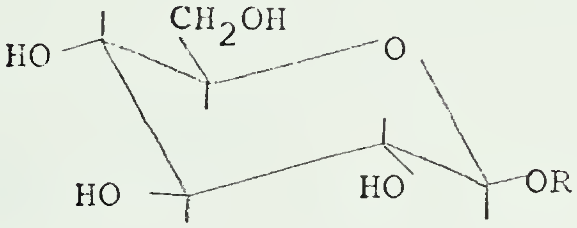
The synthesis of 3-deoxyhexoses and 3-deoxyheptoses from glycals was reported by Rosenthal and co-workers (5). For example, they brought the hydroformylation of compound I to produce epimeric 2,6-anhydro-3-deoxy-aldehydo-heptoses.


AcO
AcO
CH2OAc
O
I
Co2(CO)8
CO
H2
AcO
CH2OAc
O
AcO
CHO
AcO
CH2OAc
O
AcO
CHO

More recently, several approaches have been made to yet another synthetic route which utilizes 1,2-unsaturated sugars as starting materials. These approaches have been toward the synthesis of α-glycosides.



α-D-Glucoside

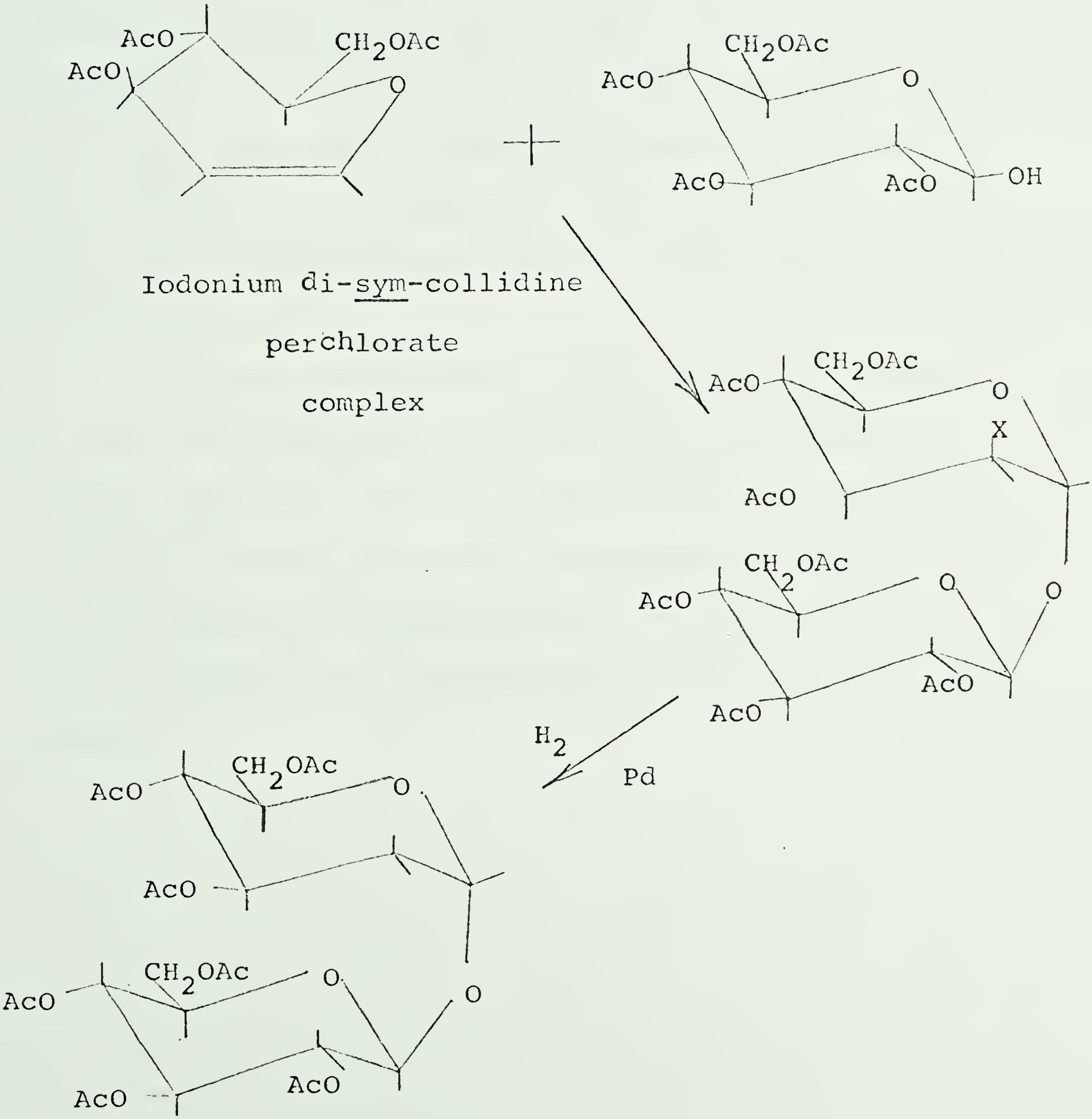


β-D-Glucoside

Such glycosides occur very widely in natural products but their synthesis has been a nagging problem in the field of carbohydrate chemistry for years. Most of the methods developed for glycoside synthesis have led to a mixture of both anomeric configurations often with the desired α-configuration formed in rather low yield. However, more encouraging results have been achieved in the synthesis which utilizes glycals as intermediates.

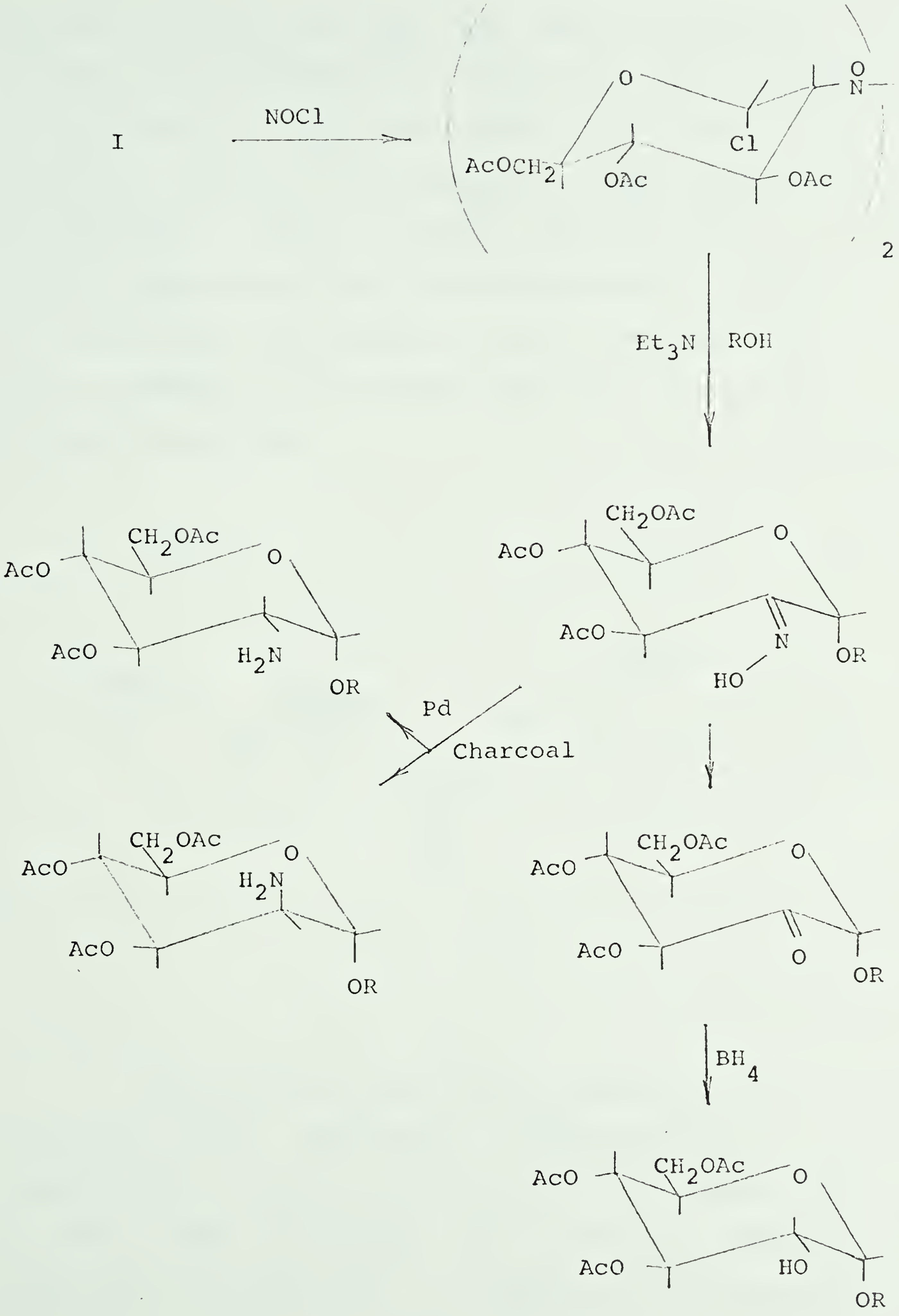
Lemieux and Morgan (6) have described a synthesis of β-D-glucopyranosyl 2-deoxy-α-D-*arabino*-hexopyranoside which involved the reaction of tri-O-acetyl-D-glucal (I)

with iodonium di-_sym_-collidine perchlorate complexes and 2,3,4,6-tetra-O-acetyl-β-glucopyranose. Initially, a 2-deoxy-2-iodo-α-D-_arabino_-hexopyranoside was formed but hydrogenolysis made the 2-deoxy-glucoside readily available.

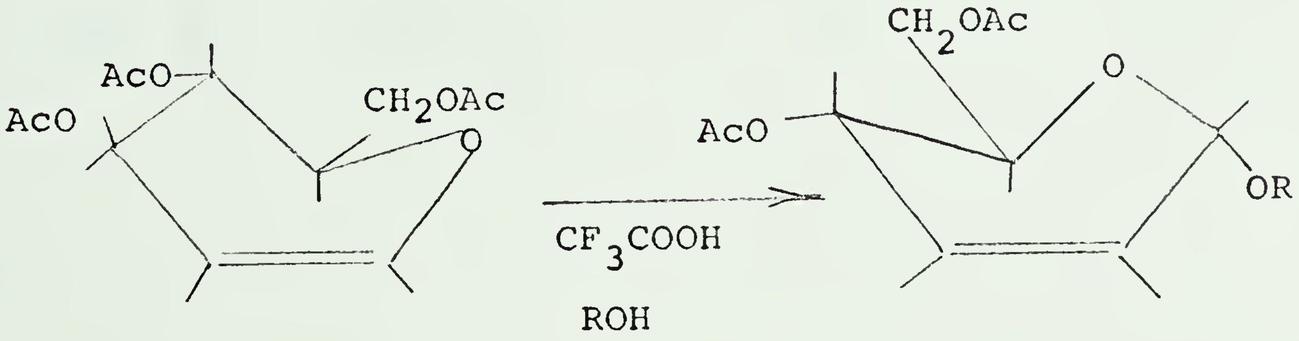

AcO
AcO
CH2OAc
O
+
CH2OAc
AcO
O
AcO
AcO
OH
Iodonium di-sym-collidine
perchlorate
complex
AcO
CH2OAc
O
X
AcO
CH2OAc
AcO
O
O
AcO
AcO
H2
Pd
AcO
CH2OAc
O
AcO
CH2OAc
AcO
O
O
AcO
AcO

The synthesis of 2-amino-2-deoxy-α-D-glucosides has been the aim of a method worked out by Lemieux, Nagabushan and O'Neill (7). These authors added nitrosyl chloride to compound I to produce a dimeric 2-deoxy-2-nitroso-α-D-glucopyranosyl chloride. Treatment of the addition product with triethylamine and then methanol resulted in the production of methyl 3,4,6-tri-O-acetyl-2-oximino-α-D-arabino-hexopyranside. Lemieux and Nagabushan (8) were able later to bring about the reduction of the oxime with effective control of the configuration created at C-2 during the reduction. In a further study (9), the method was extended to the use of several different aglycons.

A variation on this synthesis of α-glycosides has been the subject of a communication by Lemieux, Suemitsu and Gunner (10). A transoximation reaction of 3,4,6-tri-O-acetyl-2-oximino-α-D-arabino-hexopyranoside, formed as before, made available a ketoglycoside which could be reduced with borohydride to give the α-glucopyranoside.


I
NOCl
O
N
Cl
AcOCH$_2$
OAc
OAc
2
Et$_3$N
ROH
CH$_2$OAc
AcO
O
AcO
N
HO
OR
CH$_2$OAc
AcO
O
AcO
H$_2$N
OR
Pd
Charcoal
CH$_2$OAc
AcO
O
AcO
O
OR
CH$_2$OAc
AcO
O
H$_2$N
AcO
OR
BH$_4$
CH$_2$OAc
AcO
O
AcO
HO
OR

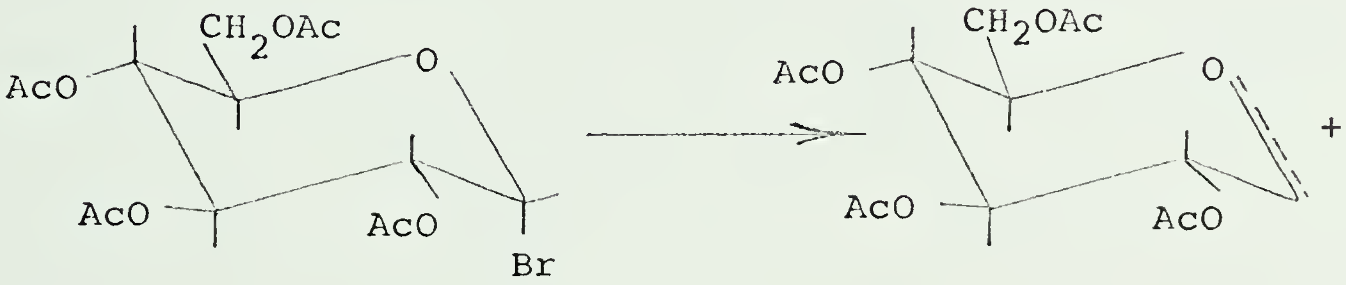
Ferrier and Prasad (11) have very recently described a method for the synthesis of α-glycosides which contain 2,3-unsaturation. Thus, for example, they treated tri-O-acetyl-D-glucal (I) with alcohols in the presence of trifluoroacetic acid as a catalyst and were able to isolate pyranosides of the α-D configuration in which the double bond had migrated to the 2,3 position. Of course, addition to this double bond has led to the saturated glycosides.



The standard method for the preparation of acetylated glycals (acetylated 1,2-dideoxy-glyc-1-enopyranoses) has been described by Roth and Pigman (12) and bears rather few changes from the original technique elaborated by Fischer (13). An acetylated glycopyranosyl bromide is treated, as a solution in cold aqueous acetic

acid, with an excess of zinc dust. The addition of copper sulfate (14) (or chloroplatinic acid (15)) as a catalyst has been the only change.

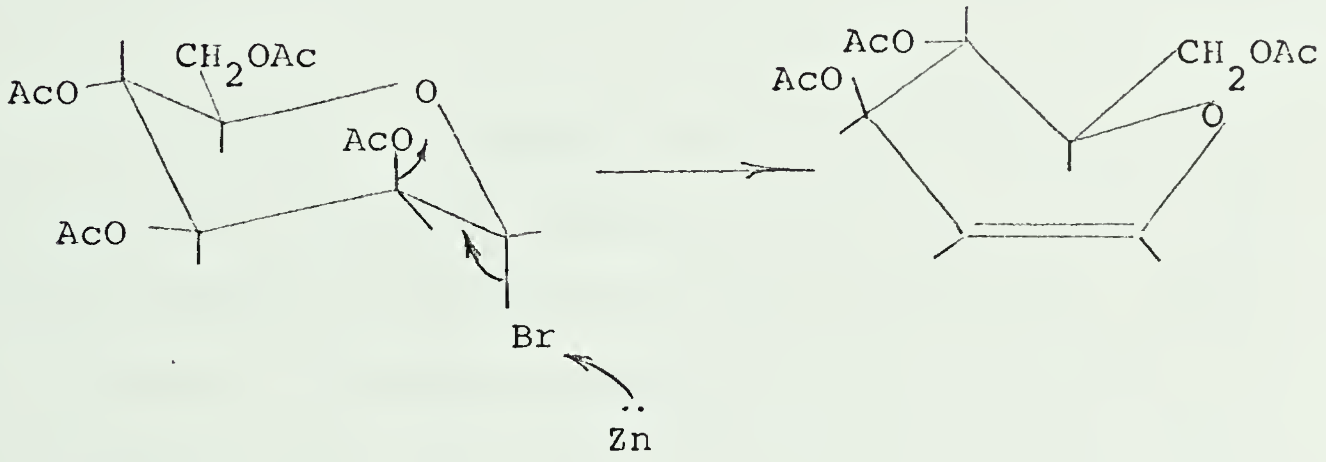
A mechanism for the reduction advanced by Overend (4) envisaged an initial heterolysis leading to a carbonium ion.



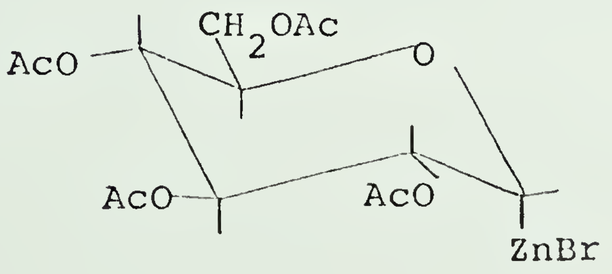
But such a mechanism was deemed improbable by Shoppee and co-workers (16) because of observations that the reaction was relatively independent of solvent and only the zinc was an essential reagent.

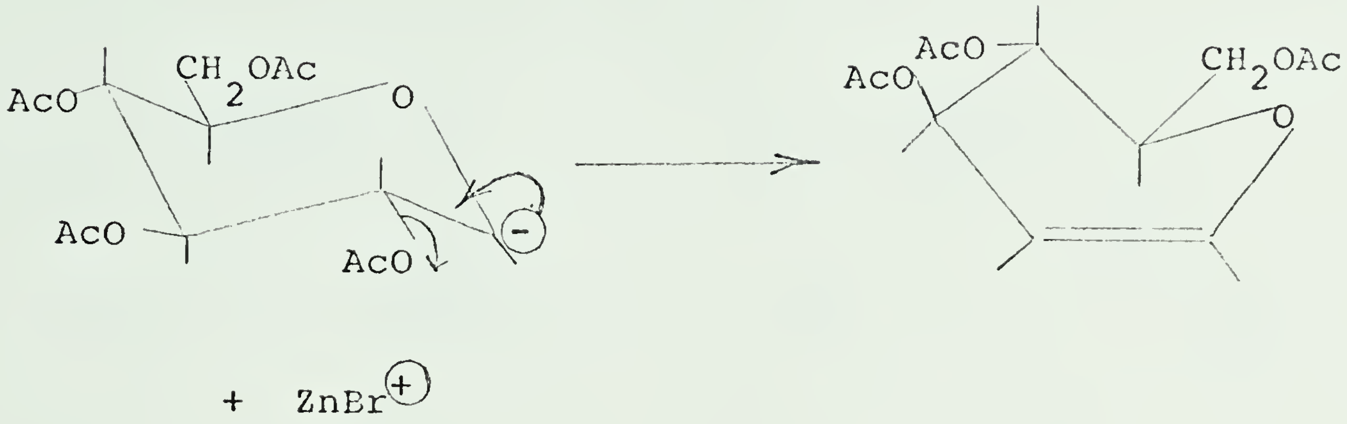
A survey of the various possible mechanisms for elimination reactions of this type was made by House and Ro (17). These authors also ruled out the carbonium ion mechanism and, in addition, they ruled out a radical intermediate since the normal radical side-reactions (coupling or solvent attack) were never observed. Also, there was

serious doubt that a radical intermediate would eliminate an alkoxy radical spontaneously. Thus, they were left with the supposition that the reaction proceeded via a short-lived organometallic or carbanionic species. They envisaged an initial nucleophilic attack on the halogen by the metal. A concerted simultaneous loss of acetate ion could lead to the glycal in a normal trans process.

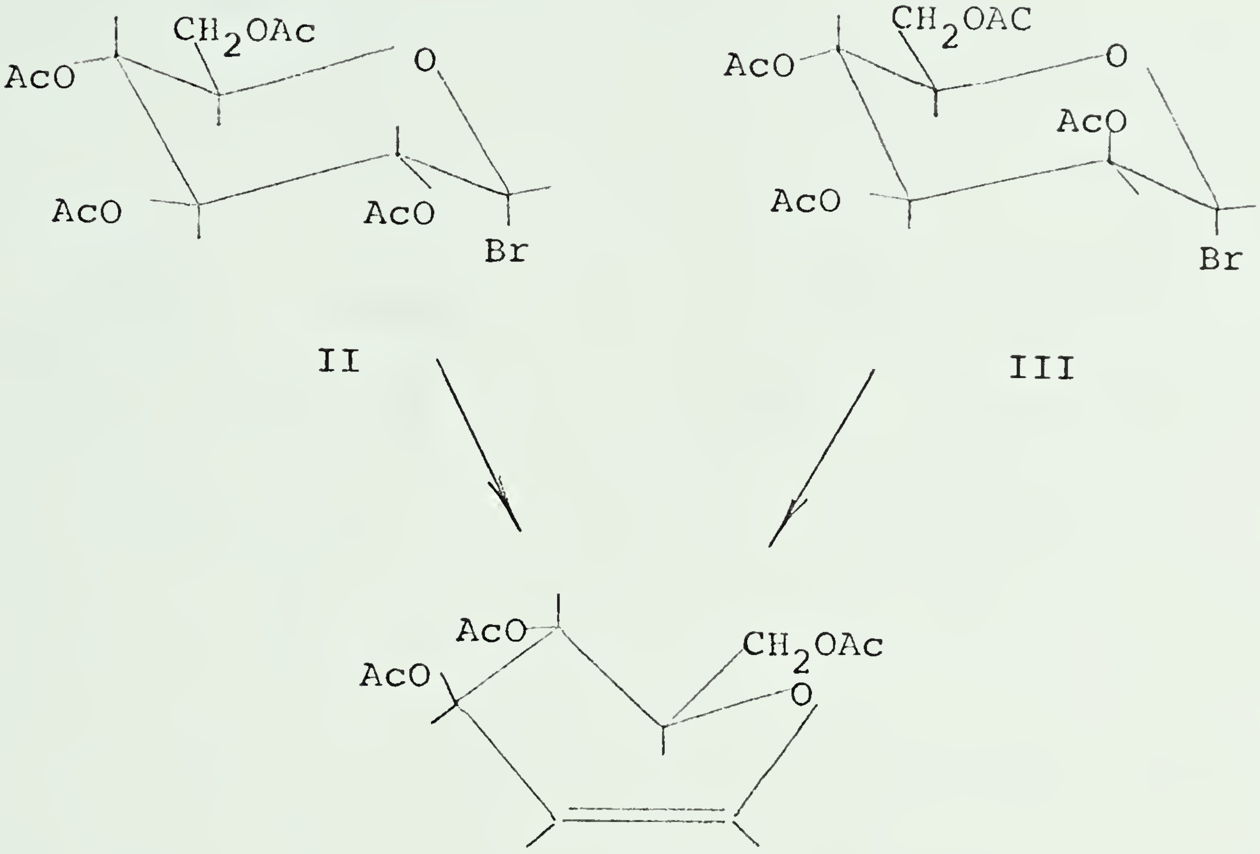

AcO
CH2OAc
O
AcO
AcO
Br
Zn
AcO
AcO
CH2OAc
O

On the other hand, where a concerted trans process was not observed or not feasible, a discrete organometallic imtermediate could form and collapse via a carbanion to the olefin.


AcO
CH2OAc
O
AcO
AcO
ZnBr



The latter mechanism would seem to be preferable for the glycal synthesis because of the demonstrated lack of stereochemical prerequisites for this reaction. Thus, tri-O-acetyl-1,2-dideoxy-D-arabino-hex-1-enopyranose has been prepared both from tetra-O-acetyl-α-D-glucopyranosyl bromide (II) (9) and from tetra-O-acetyl-α-D-mannopyranosyl bromide (III) (18). In the case of the latter, of course, a 1,2 trans elimination is possible but, in the former, the reaction must proceed in a cis fashion. This lack of prerequisite stereochemistry seems general since both members of many pairs of C-2 epimeric acetylated glycosyl bromides have been utilized in the synthesis of the corresponding glycals.


AcO
CH$_2$OAc
O
AcO
AcO
Br
AcO
CH$_2$OAC
O
AcO
AcO
Br
AcO
AcO
CH$_2$OAc
O

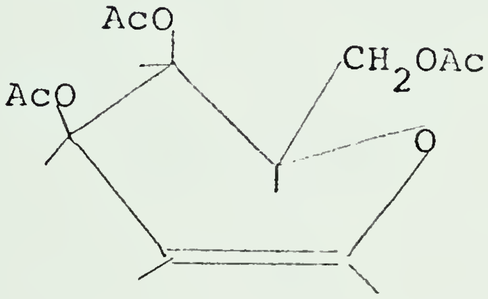
II

III

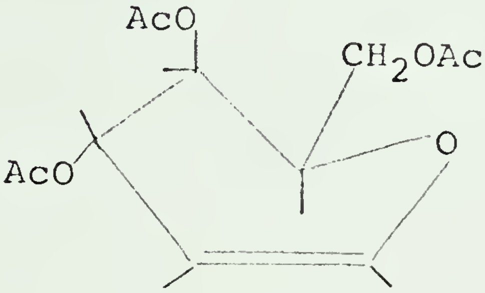
I

Three of the four possible acetylated 1,2-unsaturated hexopyranoses have been prepared by the zinc dust reduction. Compound I has been previously mentioned. Tri-O-acetyl-D-galactal (tri-O-acetyl-1,2-dideoxy-D-lyxo-hex-1-enopyranose) (IV) was first reported by Levene and Tipson (2) in 1931. While these workers were able to prepare a crystalline compound in 88 % yield, Tamm and Reichstein (19), 17 years later, were able to isolate

only 54 % of an oil. No experimental details have been reported for the preparation of tri-O-acetyl-D-gulal (tri-O-acetyl-1,2-dideoxy-D-xylo-hex-1-enopyranose) (V) claimed by Ciment and Ferrier (20).



IV

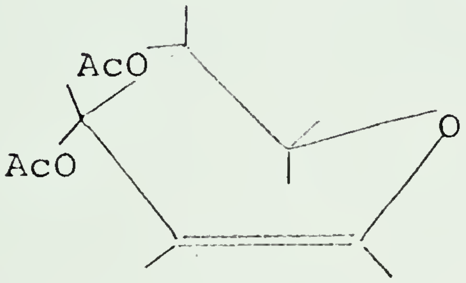


V

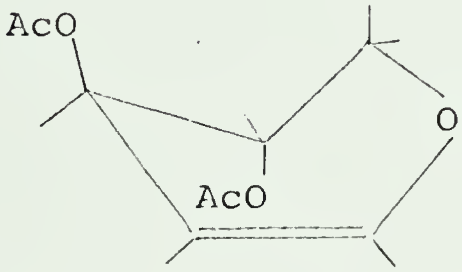
Derivatives of D-allal (tri-O-acetyl-1,2-dideoxy -D-ribo-hex-1-enopyranose) (VI) have been prepared by another route which is mentioned separately.

In the pentopyranose series, with two pairs of C-2 epimers, there two possible 1,2-unsaturated compounds. Both of these have been synthesized several times in both the D and the L configuration. Di-O-acetyl-D(L)-arabinal (di-O-acetyl-1,2-dideoxy-D(L)-erythro-pent-1-enopyranose) (VII) has been prepared in yields varying from 57 % (21) to 72 % (22). On the other hand, di-O-acetyl-D(L)-xylal

(di-O-acetyl-1,2-dideoxy-D(L)-threo-pent-1-enopyranose) (VIII) has been synthesized in yields from 37 % (23) to 80 % (24).

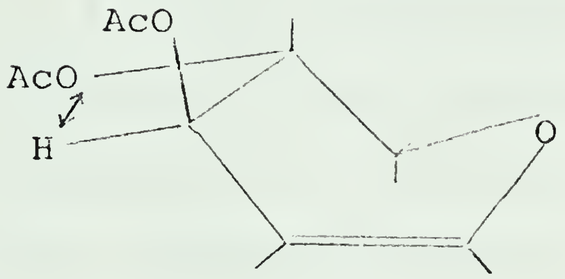


VII



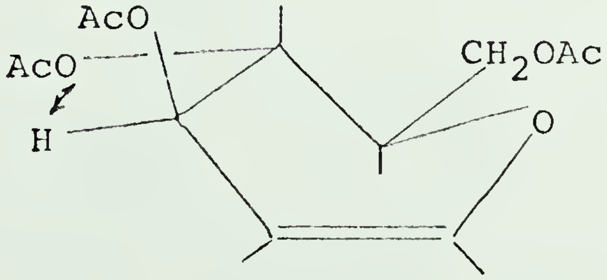
VIII

A number of n.m.r. studies of acetylated glycals have been reported (25,26). In all cases, the $J_{1,2}$ is in the range (5.9 - 6.5 Hz) as expected for a cis olefin. Those glycals derived from the pentoses appear to exist in half chair conformations. Di-O-acetyl-1,2-dideoxy-D-threo-pent-1-enopyranose (VIII) has both acetoxy groups in a quasi axial orientation and this has been assigned to the $A^{(1,2)}$ effect (27) involving the interaction between H-3 and the 4-acetoxy group when the latter is in the equatorial orientation.



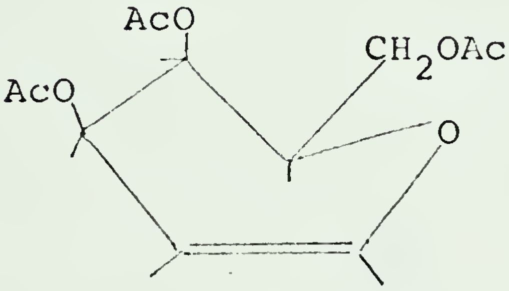
VIII

The glycals derived from hexoses are anchored more strongly in the half-chair conformation which has the bulky acetoxymethyl group in the equatorial orientation and for this reason the $A^{(1,2)}$ effect is not strong enough to be the cause of a change in the ring conformation.

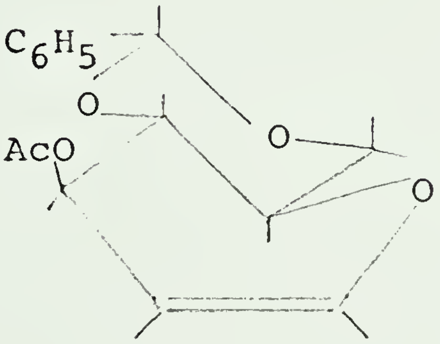


I

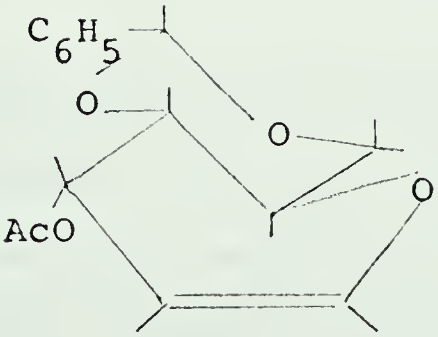
Thus, tri-O-acetyl-1,2-dideoxy-D-arabino-hex-1-enopyranose (I) was analyzed as a slightly distorted half-chair on the basis of studies of allylic coupling constants ($J_{1,3}$) as first elaborated by Garbisch (28). The coupling patterns of tri-O-acetyl-1,2-dideoxy-D-lyxo-hex-1-enopyranose (IV) were also found to be in agreement with a slightly distorted H1 conformation.


AcO
AcO
CH$_2$OAc
O

IV

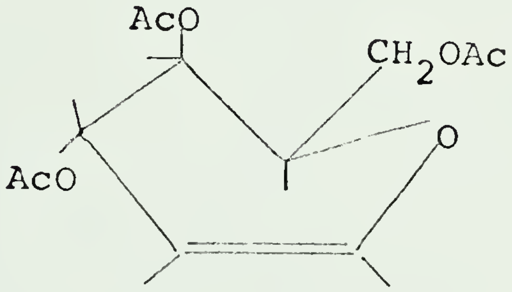

C$_6$H$_5$
O
O
AcO
O

IX


C$_6$H$_5$
O
O
O
AcO

X

The theoretical relationships used were determined by the assumption of an H1 conformation for 4,6-O-benzylidene-1,2-dideoxy-D-arabino-hex-1-enopyranose (IX) (29) and 4,6-O-benzylidene-1,2-dideoxy-D-ribo-hex-1-enopyranose (X) (30). This assumption could be made because of the constraints applied by the fusion of the benzylidene function to the unsaturated ring. No determination of conformation has been made for tri-O-acetyl-1,2-dideoxy-D-xylo-hex-1-enopyranose (V) but this compound reasonably can be assumed to take up a similar molecular shape.

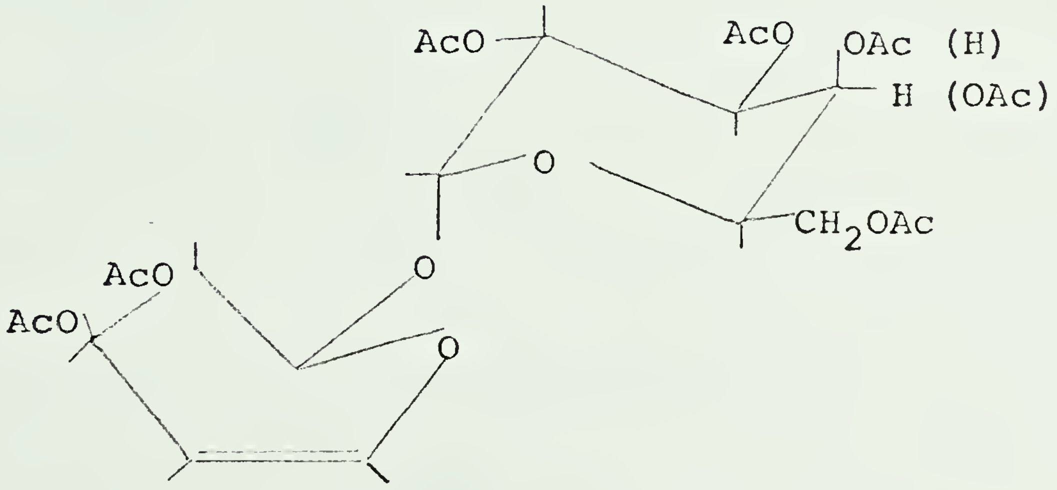


V

All of the glycals mentioned above have been derivatives of aldoses. Only two examples of ketose-related glycals have been reported and both of these are in the hexose series. Neither was produced by the reduction of an acetohalogeno sugar but rather by a

method which will be discussed separately.

Proceeding to the disaccharides, one finds five examples of 1,2-unsaturated compounds in the literature. All of these are, in fact, hexopyranosyl substituted D-glucals. Hexa-O-acetylmelibial [3,4-di-O-acetyl-1,2-dideoxy-6-O-(tetra-O-acetyl-α-D-galactopyranosyl)-D-arabino-hex-1-enopyranose] (XI) has been prepared by Levene and Jorpes (31) with no mention of yield.

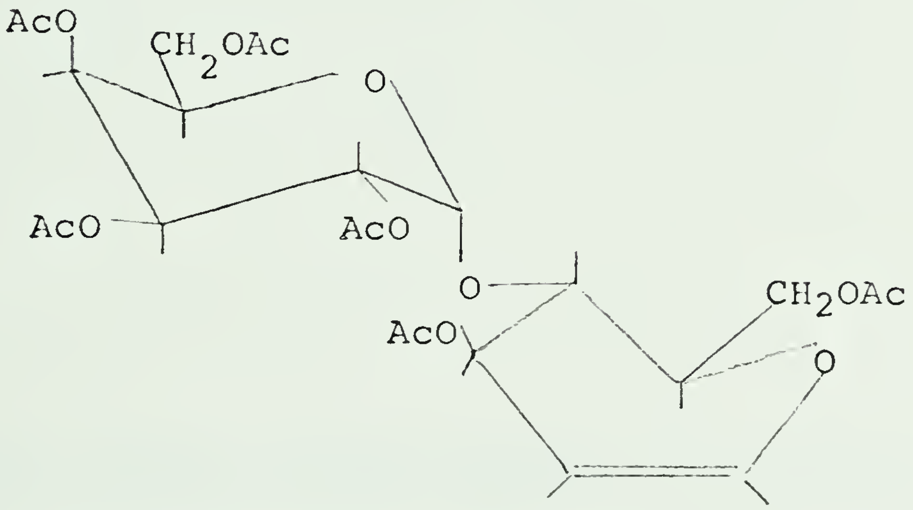


XI (XII)

The corresponding 6-O-α-D-glucopyranosyl substituted compound, hexa-O-acetylgentiobial (XII) has been reported twice.

Dauben and Evans (32) claimed to have isolated the compound in 90% yield whereas Bergmann and Freudenberg (33) in the original work, were able to isolate only 50%.

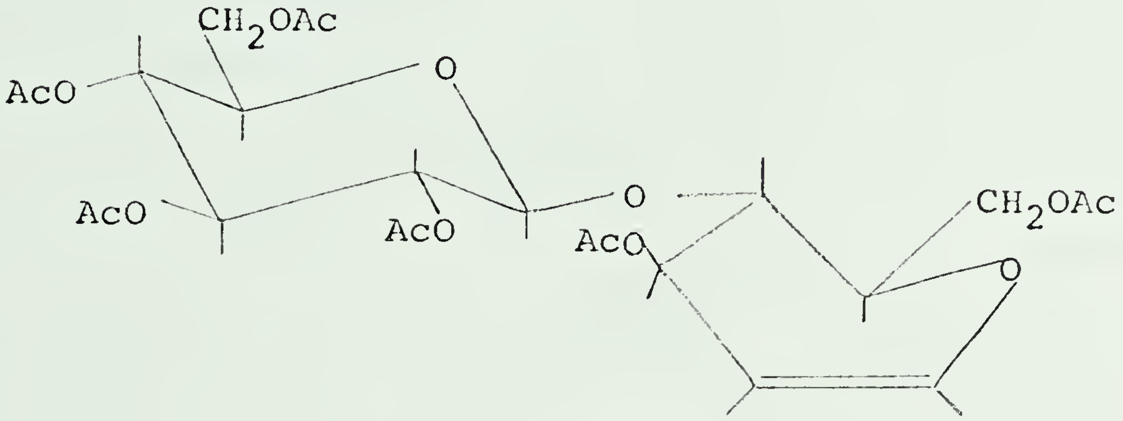
Hexa-O-acetyllactal [3,6-di-O-acetyl-1,2-dideoxy-4-O-(tetra-O-acetyl-β-D-galactopyranosyl)-D-arabino-hex-1-enopyranose] (XIII) has been prepared in yields ranging from 50% (34) to 77% (35).



XIII

The final two examples are 4-O-D-glucopyranosyl-D-glucals. Hexa-O-acetyl-cellobial (XIV) contains the so-called β-linkage between the monosaccharides while hexa-O-acetyl-maltal (XV) has the α-linkage. The

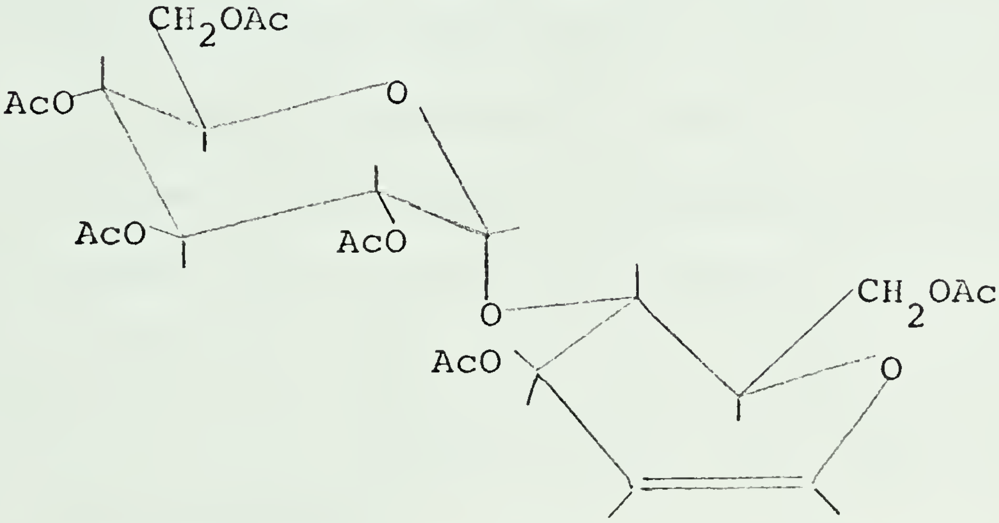
former compound has been prepared four times with Fischer and Fodor (36) laying claim to the original work.



XIV

Hexa-O-acetyl maltal [3,6-di-O-acetyl-1,2-dideoxy-4-O-(tetra-O-acetyl-α-D-glucopyranosyl)-D-arabino-hex-1-enopyranose] (XV) has also been subject to four preparations. Again it was from Fischer's laboratory (37) that the original work emanated and a 50% yield was achieved. Bergmann and Kobel (38) had claimed to have prepared the compound one year earlier but their report has been shown to be incorrect by Haworth, Hirst and Reynolds (39) who found that the earlier workers had isolated an acetylated maltose. The

last report of D-maltal was by Gakhokidze (40) who was able to increase the yield in the reduction to 70% in 1948.

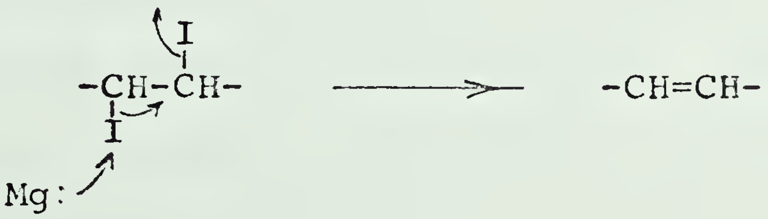


XV

While the zinc dust reduction of acetobromosugars in acetic acid seems to have found wide application, the problems of the method are obvious. At best, it is erratic and different workers report widely variant yield values in exactly correspondent reactions. Part of this inefficiency might be due to the relative instability of the starting materials but, in most cases, these were utilized in a crystalline state.

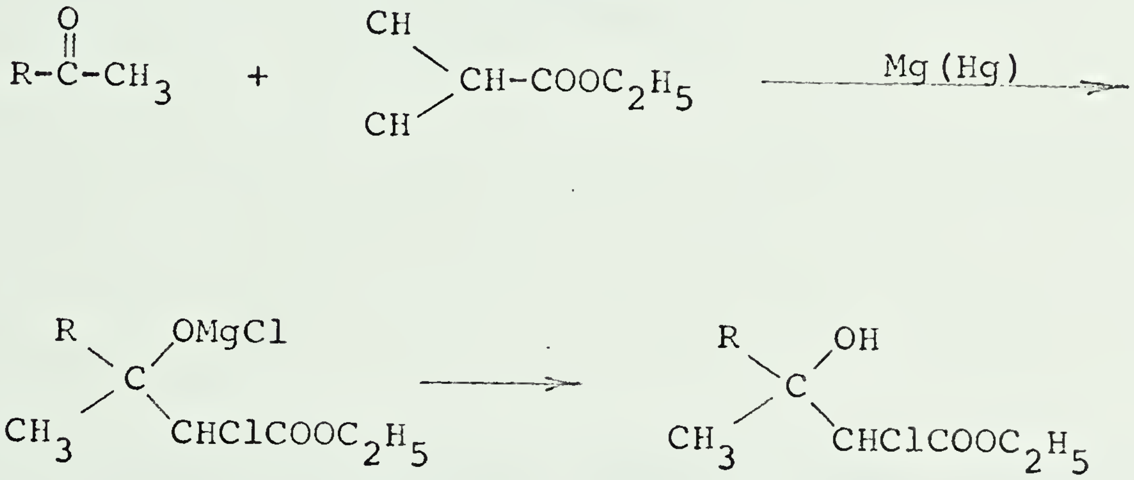
A second problem is the danger to easily hydrolysable linkages through long contact with aqueous acetic acid. Certainly reaction times of up to four hours make the technique rather inadvisable for many types of carbohydrate derivatives. Although the method has been applied to disaccharides, one would be somewhat worried about the hydrolysis of glycosidic linkages. This would be a major problem in any material containing a fructofuranose structure since the fructofuranosyl linkage is hydrolysed a factor of 1000 times faster (41) than the glucopyranosyl linkages which, to date, have been treated in the zinc dust reduction.

An answer to many of these problems would be the application of a more reactive metallic reducing agent and one is led to consider magnesium because of its long history in organometallic chemistry. The metal is well known in the production of Grignard reagents from organic halides and it has been utilized often in the dehalogenation of vicinal dihalides (42).



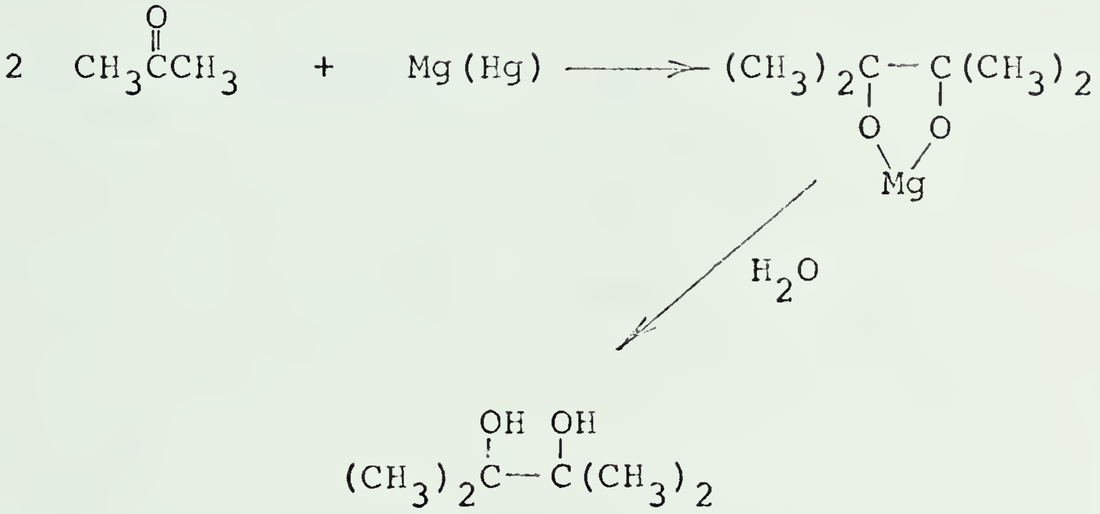
Amalgamated magnesium was chosen for the present work because of its even greater reactivity.

Magnesium amalgam has not received a lot of attention in the organic chemical literature. Darzens (43,44) has reported the use of the material in the condensation of ethyl dichloroacetate with aldehydes and ketones.

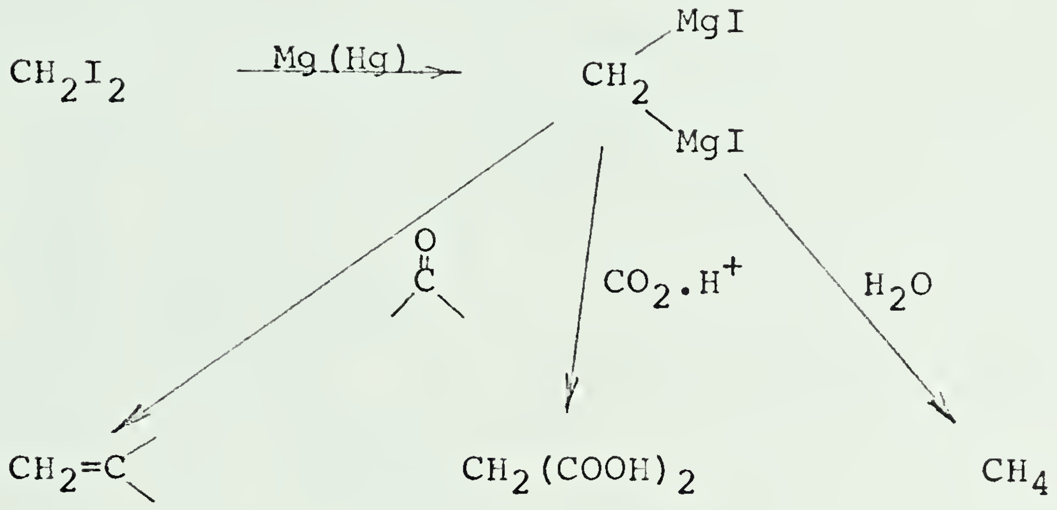

R-C-CH3
O
+
CH
CH
CH-COOC2H5
Mg (Hg)
R
OMgCl
C
CH3
CHClCOOC2H5
R
OH
C
CH3
CHClCOOC2H5

R=CH_3, C_6H_5

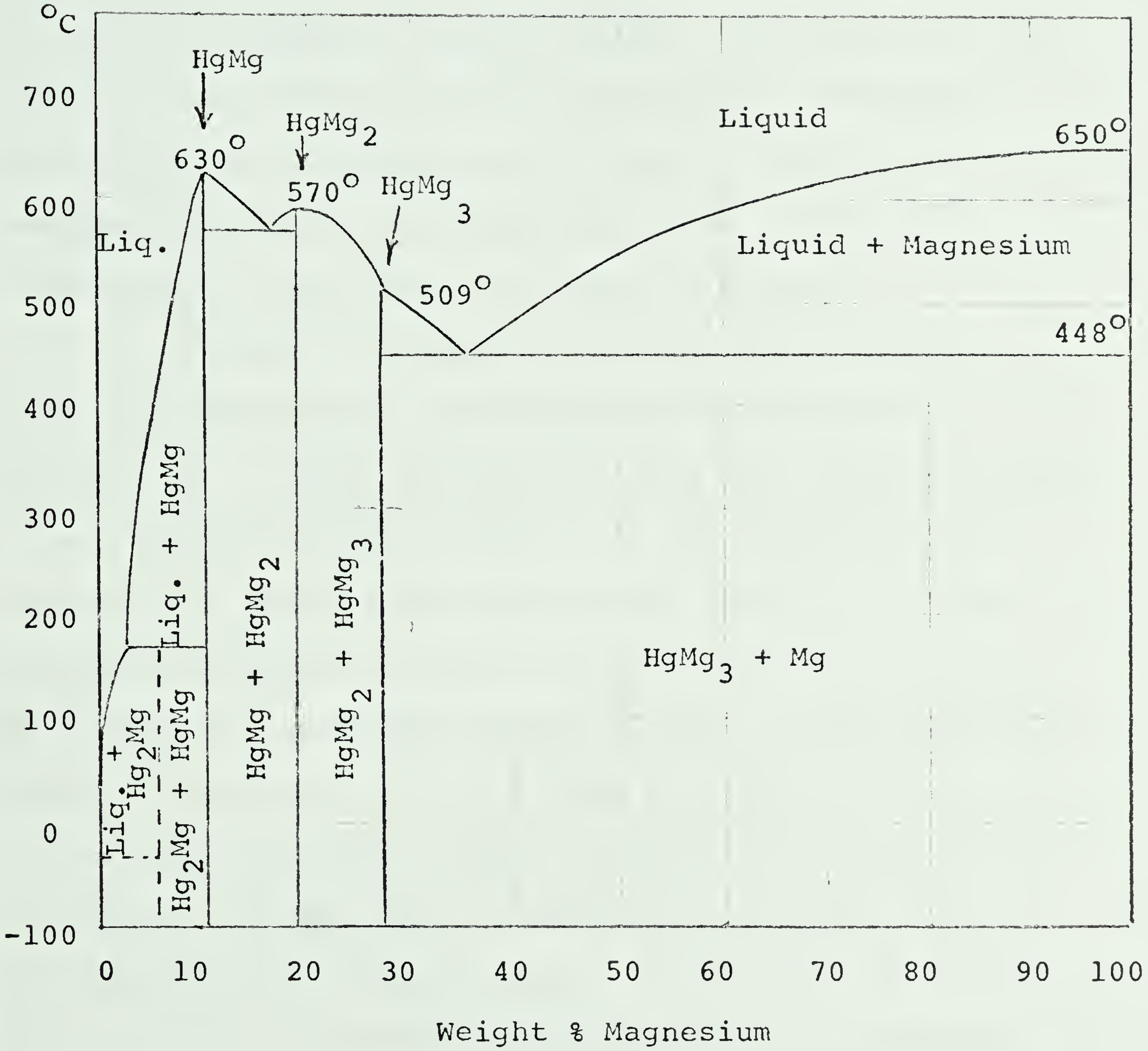
A standard method for the production of pinacol hydrate reported by Adams and Adams(45) involves the reaction of amalgamated magnesium with acetone. These authors prepared the amalgam *in situ* through reaction of magnesium with mercuric chloride.


2
$CH_3\overset{O}{\overset{\|}{C}}CH_3$
+
Mg(Hg)
$(CH_3)_2C - C(CH_3)_2$
O
O
Mg
H_2O
OH OH
$(CH_3)_2C - C(CH_3)_2$

Finally, in a publication which appeared during the course of this work, Cainelli, Bertini, Grasselli and Zubiani (46) demonstrated the usefulness of magnesium amalgam in the preparation of gem-dimetallic compounds.



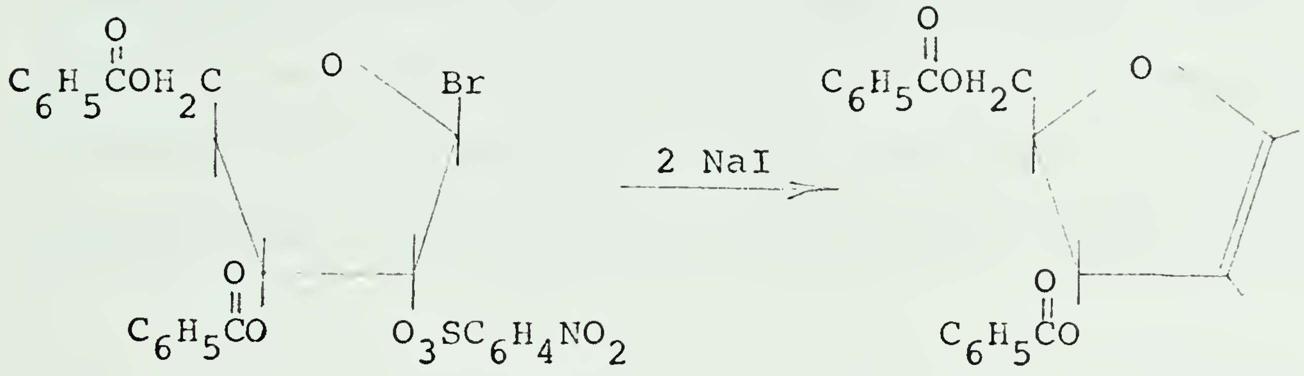
Two forms of amalgamated magnesium are readily available to the organic chemist: a solid compound which has been reported to bear the formula Hg_2Mg (47) and a liquid solution containing lesser amounts of magnesium. In this investigation, solid magnesium amalgam was prepared by the method of Berglund and Sillen (48). This merely involved heating calculated amounts of the two metals in vacuo to produce a homogeneous solid. Because of the sensitivity of the amalgam to oxygen and moisture, precautions similar to those utilized in the handling of sodium metal were necessary.


°C
700
600
500
400
300
200
100
0
-100
HgMg
630°
HgMg$_2$
570°
HgMg$_3$
509°
Liquid
650°
Liq.
Liquid + Magnesium
448°
Liq. + HgMg
HgMg + HgMg$_2$
HgMg$_2$ + HgMg$_3$
HgMg$_3$ + Mg
Liq. + Hg$_2$Mg
Hg$_2$Mg + HgMg
0
10
20
30
40
50
60
70
80
90
100
Weight % Magnesium

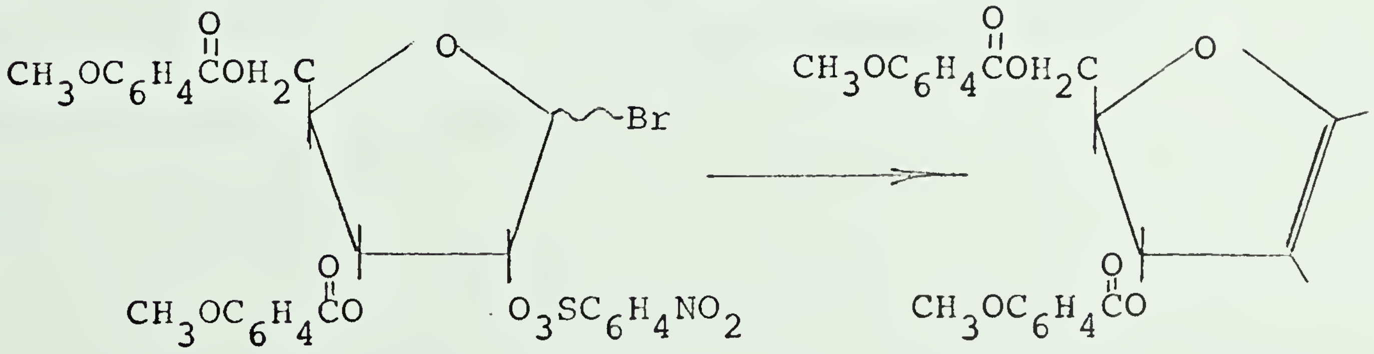
(102)

N,N-Dimethylformamide (DMF) was chosen as the solvent in the reduction for three reasons. As a non-hydroxylic solvent, it could not become involved in solvolysis reactions with the rather labile acetylated glycosyl bromides. This latter reaction was thought to be a major reason for the low yields often found with the zinc dust and aqueous acetic acid method. Similarly, DMF was relatively stable with respect to magnesium amalgam and finally, DMF has been shown to be a good solvent for a wide range of organic compounds.

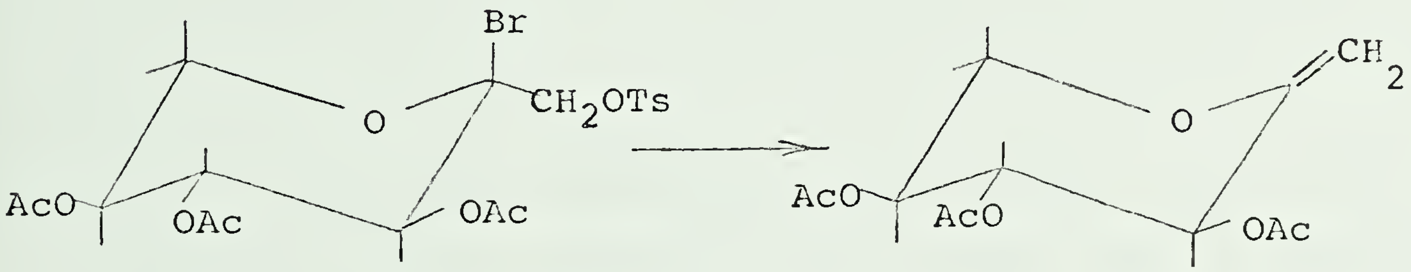
A second approach to the synthesis of 1,2-unsaturated compounds from glycopyranosyl bromides represented a complete departure from the former procedure. It was hoped to apply a method for the introduction of unsaturation which had received much attention in the carbohydrate field but had not found application in the synthesis of aldohexose-related glycals. This method was based on the action of a solution of sodium iodide on structures containing vicinal disubstitution consisting of either a halogen and a substituted sulfonyl group or two substituted sulfonyl groups. Thus, Ness and Fletcher (49) were able to produce 3,5-di-O-benzoyl-1,2-dideoxy-D-*erythro*-pent-1-enofuranose from the 2-O-*p*-nitrophenylsulfonyl-β-D-ribosyl bromide using a 10% solution of sodium iodide in acetone at 5° for four hours.



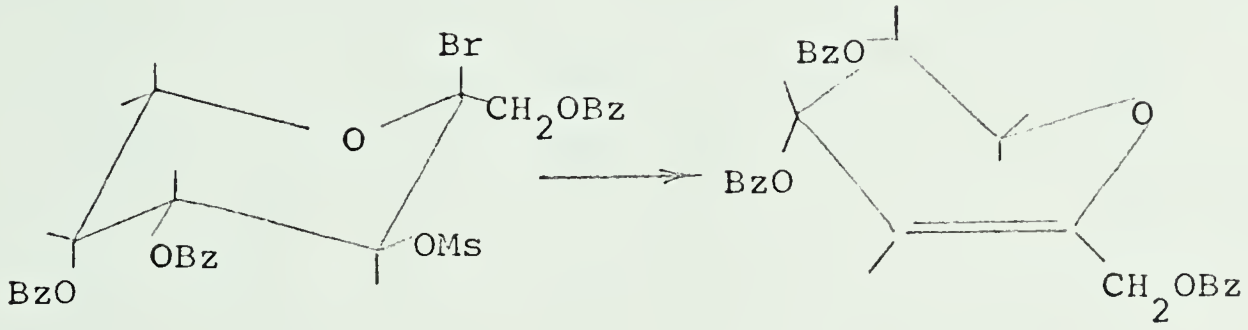
Haga and Ness (50) reported similar results with the corresponding 3,5-di-O-*p*-anisoyl compound.



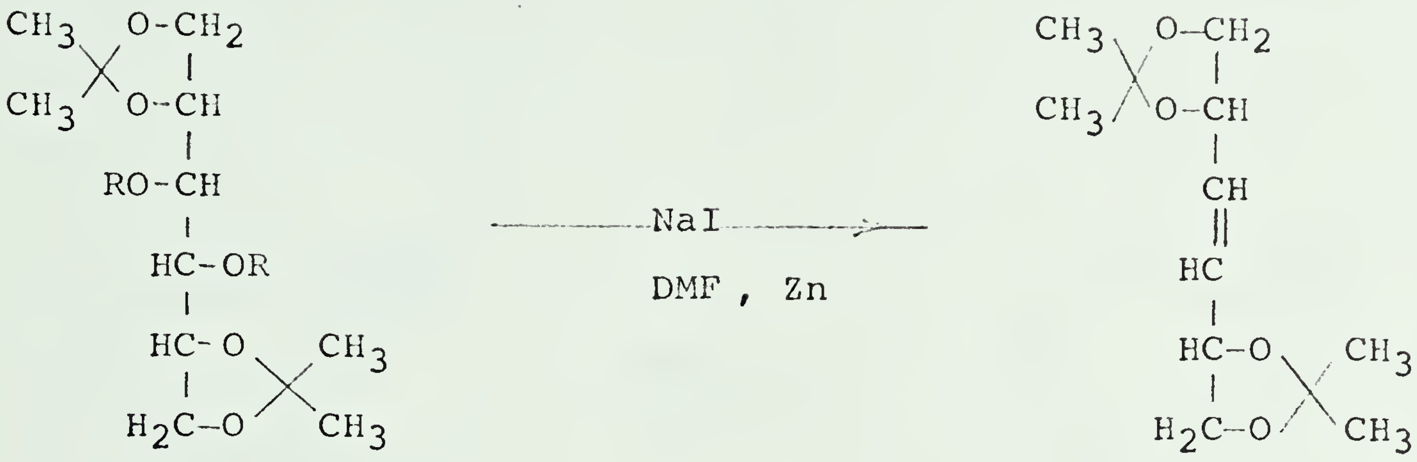
It was by this method that the two known ketose-related glycals have been produced. By the treatment of 3,4,5-tri-O-acetyl-2-bromo-2-deoxy-1-O-p-toluenesulfonyl-α-L-sorbopyranose with sodium iodide, Tokuyama, Tsujino and Kiyokawa (51) were able to synthesize a 1,2-unsaturated-L-sorbose in a pyranoid structure containing an exocyclic double bond. This compound is not a true glycal, however a



ketose-related glycal containing an endocyclic double bond became available very recently when Ness and Fletcher (52) treated 1,4,5-tri-O-benzoyl-3-O-methanesulfonyl-β-D-fructopyranosyl bromide in similar fashion.

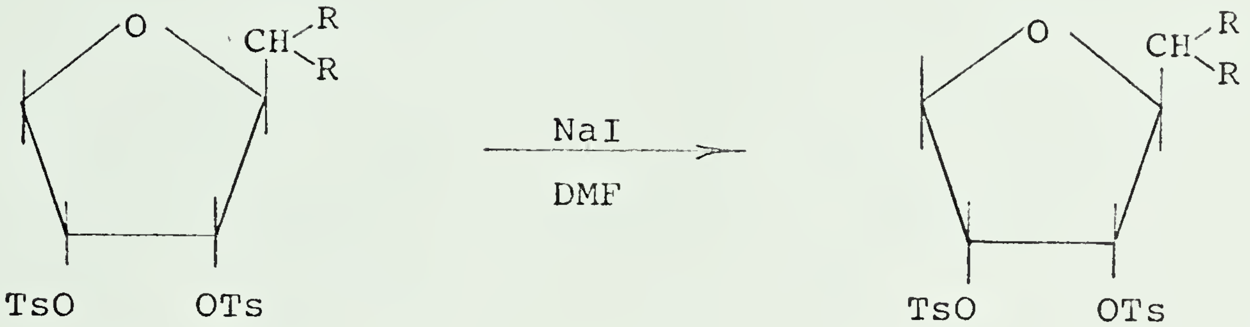


The other variation of this method, that is the use of two vicinal sulfonyl groups rather than a sulfonyl and a bromide residue, has been the subject of two publications. Tipson and Cohen (53) treated the 3,4-di-methanesulfonate (and di-*p*-toluenesulfonate) of di-O-isopropylidene-D-mannitol with an N,N-dimethylformamide solution of sodium iodide to bring about the formation of 1,2:5,6-di-O-isopropylidene-*trans*-3-hexene-D-*threo*-1,2,5,6-tetrol.

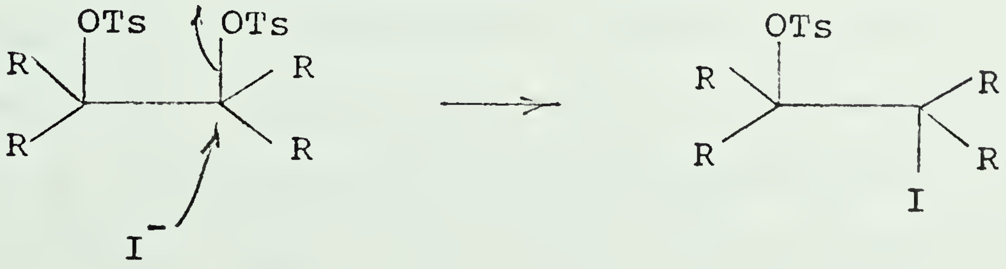


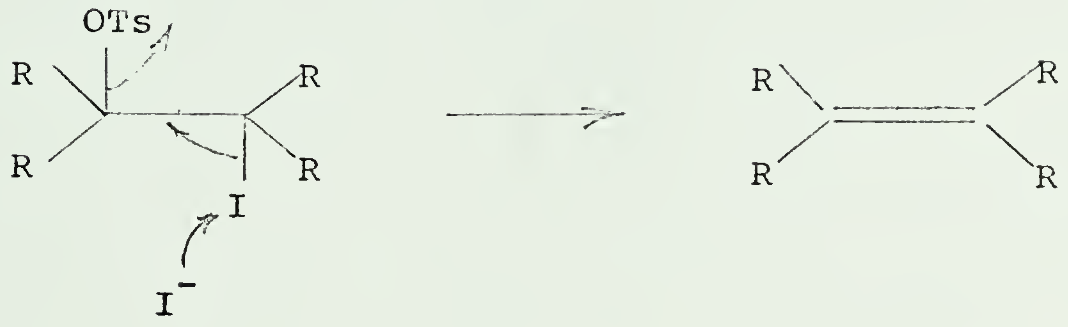
R = OMs, OTs.

Defaye and Hildesheim (54) carried out a similar reaction on a vicinal di-p-toluenesulfonate in the tetrahydrofuran series. It should be noted that in both of these cases, the reactions were carried out in the presence of zinc dust which acted as a scavenger for the iodine produced as a by-product. The removal of the iodine prevented the formation of vicinal di-iodides from the product olefins.

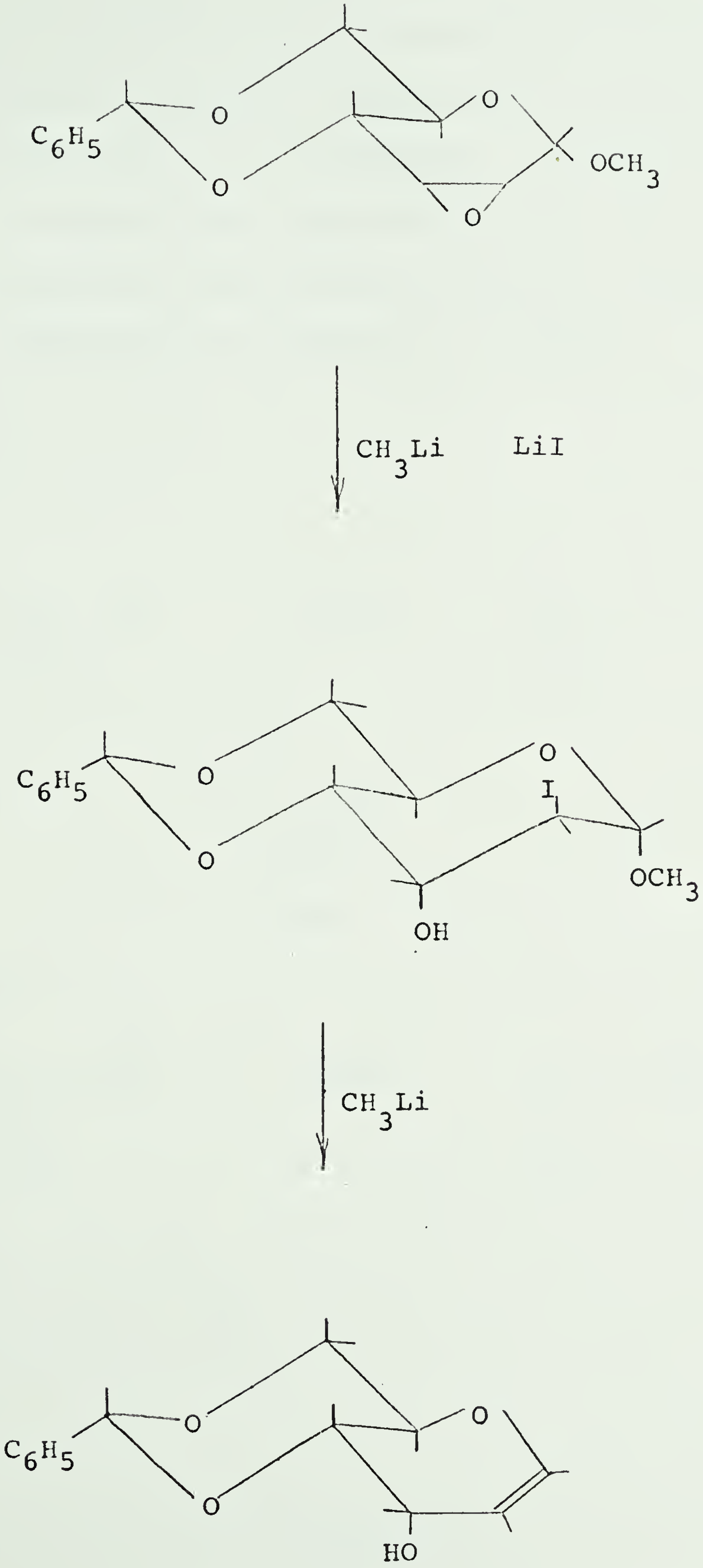

O
CH
R
R
NaI
DMF
TsO
OTs

The mechanisms of these reactions are similar and involve initial replacement of one of the substituents (sulfonyl or bromide) by iodide.

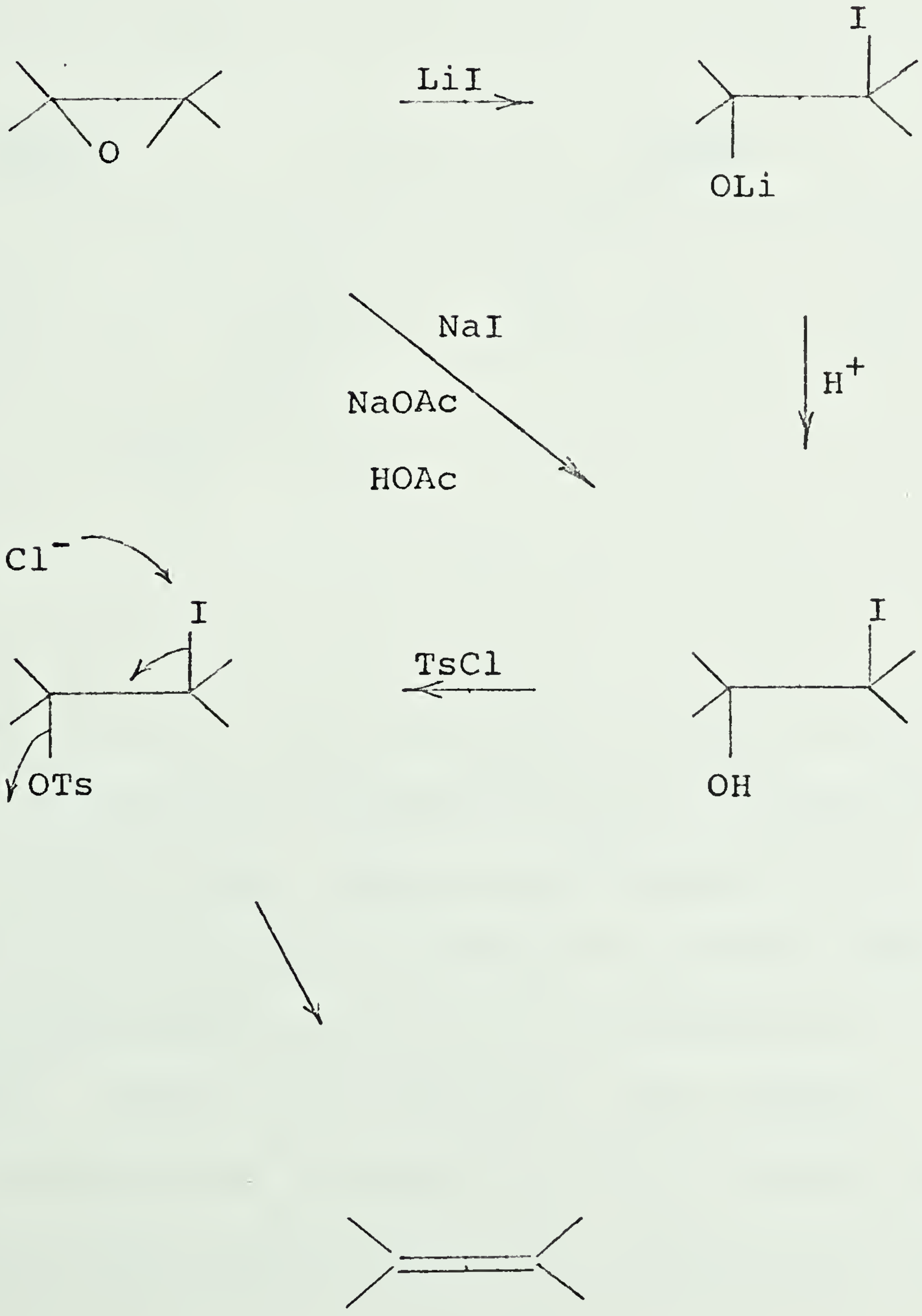




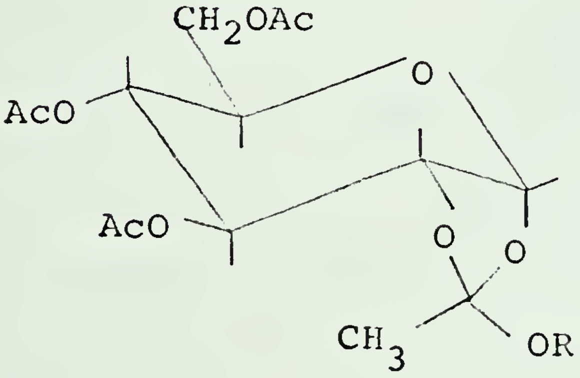
A mechanism very similar to this has been described by Lemieux, Fraga and Watanabe (55) for the preparation of 4,6-O-benzylidene-D-allal (4,6-O-benzylidene-1,2-dideoxy-D-*ribo*-hex-1-enopyranose) reported by Feast, Overend and Williams (56). These latter authors treated methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside with methyl lithium in diethyl ether and isolated the unsaturated sugar. The former authors were able to isolate the intermediate iodohydrin.

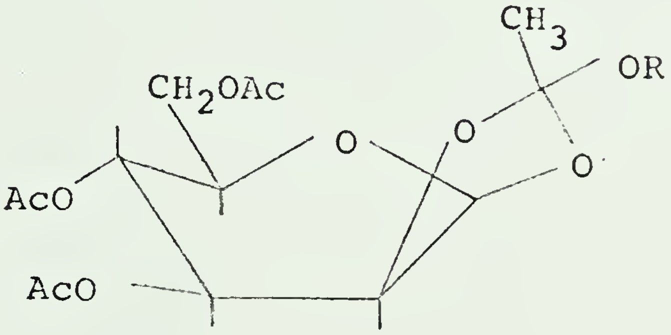

C6H5
O
O
O
O
OCH3
CH3Li
LiI
C6H5
O
O
O
I
OCH3
OH
CH3Li
C6H5
O
O
O
HO

Lemieux and co-workers (55) also found that lithium iodide could be utilized to open the epoxide with formation of the lithium alkoxide of the iodohydrin. Treatment of this and other iodohydrins with p-toluenesulfonyl chloride yielded the expected iodo-p-toluenesulfonate, which in many cases immediately collapsed to the olefin


O
LiI
I
OLi
NaI
NaOAc
HOAc
H+
Cl-
I
OTs
TsCl
I
OH

The application of deiodosulfonylation reaction to the preparation of aldose-related glycals required the synthesis of the proper 1,2-di-O-p-toluenesulfonyl compounds. In the hexopyranose series, this in turn necessitated the synthesis of compounds bearing substitution at the 3,4 and 6 positions. These were made available by the use of acetylated hexopyranose 1,2-(alkyl orthoacetates).

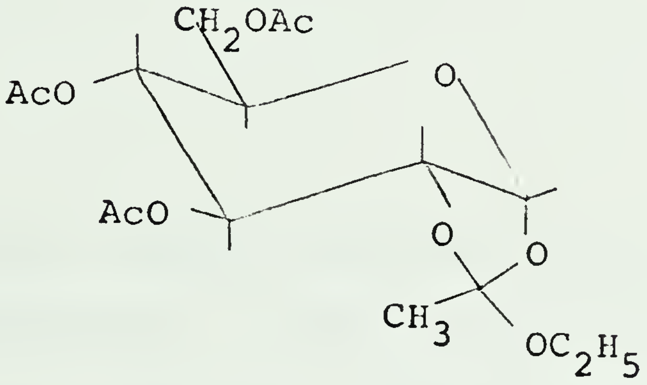




Much interest has been shown in recent years in the use of carbohydrate orthoacetates as intermediates in synthetic applications. Lemieux and Morgan (57,58) elucidated the mechanism of formation of these compounds and demonstrated their utility in the preparation of α-glycosides. Franks and Montgomery (59) recently extended the glycoside synthesis into the mannose configuration but it was Perlin (60,61) who carried out the

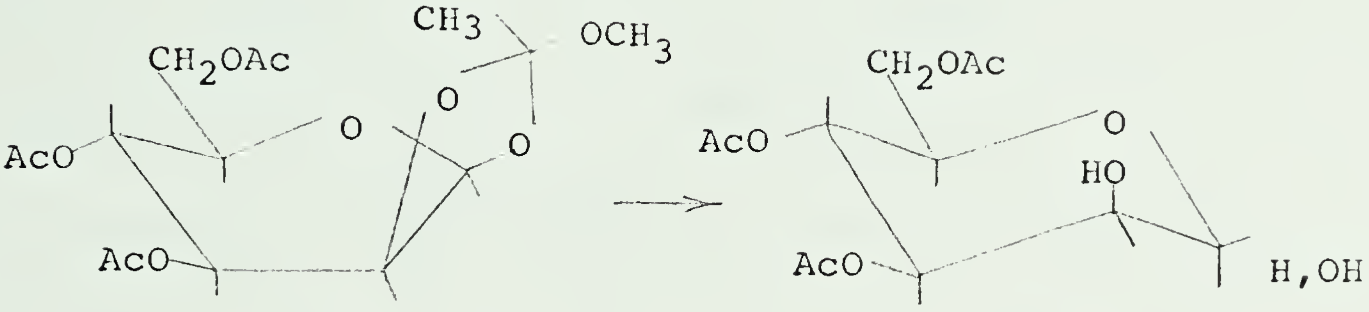
definitive work with the mannose orthoesters.

These orthester compounds have not, as yet, found apt description in standardized carbohydrate nomenclature (62,63). As a result, a nomenclature is utilized here which is correspondent to one applied by Detert (64) in description of such compounds. Thus, for example, compound XVI has been labelled: tri-O-acetyl-1,2-O-(1-exo-ethoxyethylidene)-α-D-glucopyranose.



XVI

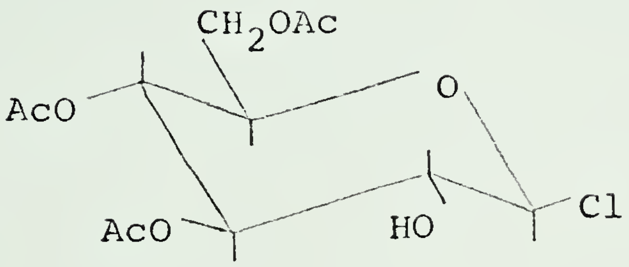
In an investigation of the "methanolysis" of tri-O-acetyl-1,2-O-(1-methoxyethylidene)-β-D-mannopyranose (XVII) , Perlin (65) found the major product to be 3,4,6-tri-O-acetyl-D-mannopyranose (XVIII).

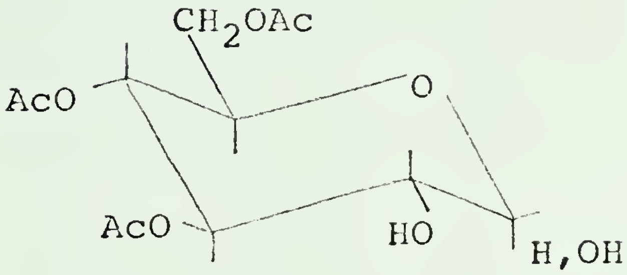

CH3
OCH3
CH2OAc
AcO
O
O
O
AcO
CH2OAc
AcO
O
HO
AcO
H,OH

XVII

XVIII

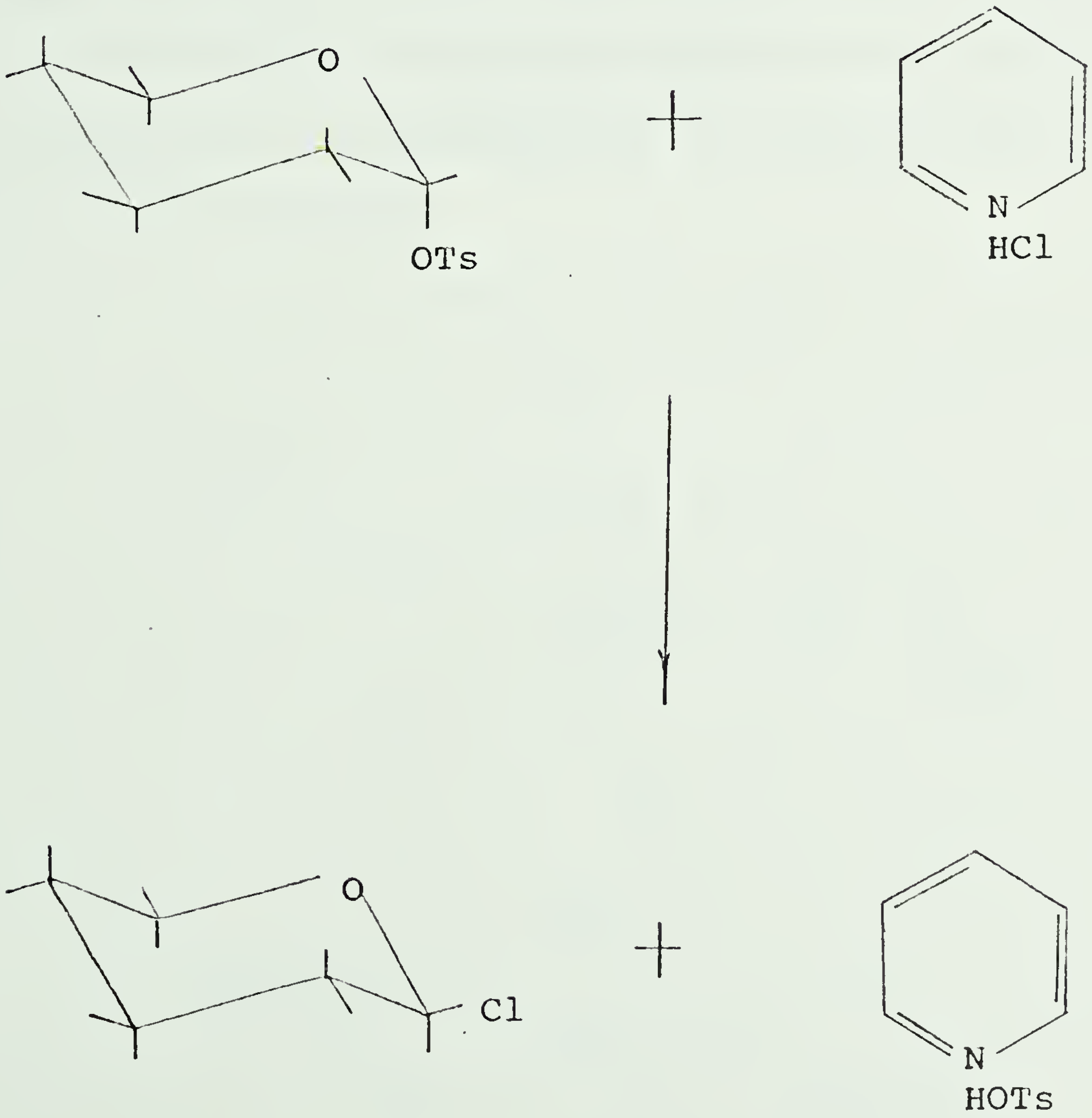
He also found similar results but with smaller yields in the gluco configuration. These 3,4,6-tri-O-acetyl-hexopyranoses have not been the subject of much attention in the past. In fact, Perlin's synthesis seems to be the only one other than that reported by Brigl and Schinle (66) which consisted of a hydrolysis reaction of 3,4,6-tri-O-acetyl-β-D-glucopyranosyl bromide.



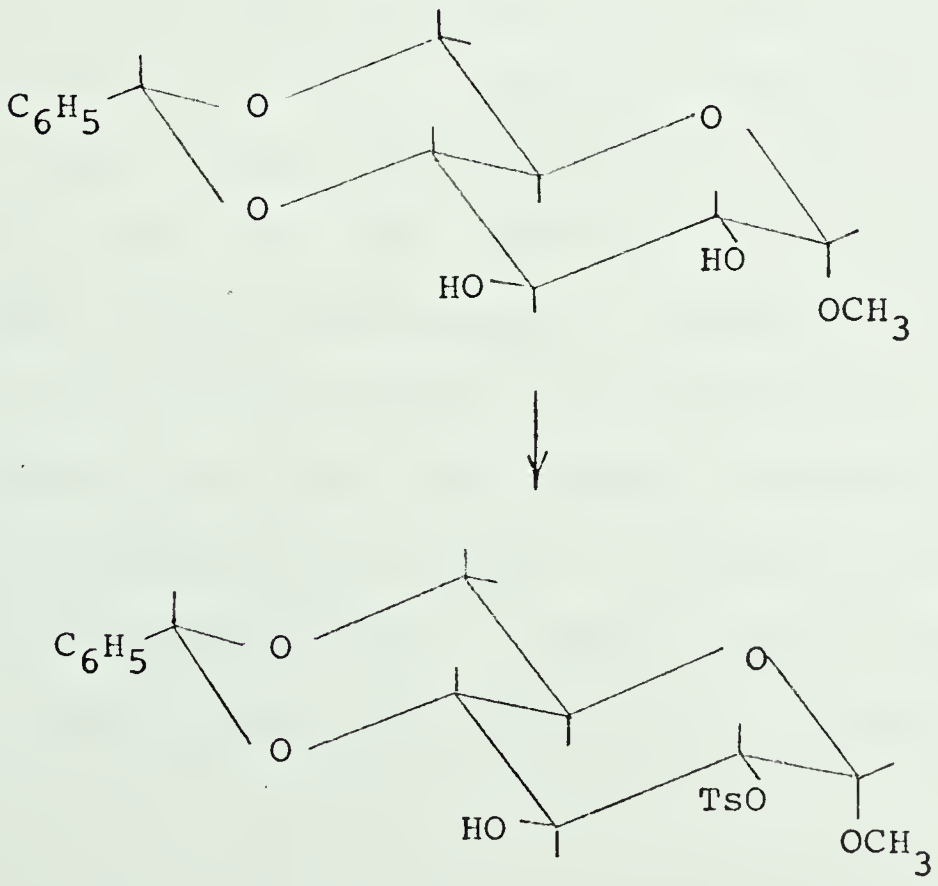


The preparation of a 1,2-di-O-*p*-toluenesulfonyl derivative from the 3,4,6-tri-O-acetyl-hexopyranoses was expected to represent a problem since previous attempts at a synthesis of a carbohydrate 1-O-*p*-toluenesulfonyl derivative by Helferich and Gnuchtel (67), for example, had led to the isolation of a 1-chloro-1-deoxy-sugar. This behaviour has been ascribed (68) to reaction of the sulfonyloxy group at the anomeric centre with pyridine hydrochloride. This latter is a by-product in the normal reaction of *p*-toluenesulfonyl chloride with sugar hydroxylic groupings to form the *p*-toluenesulfonate. In order to by-pass this problem, the attention in this work was

turned to the anhydride of p-toluenesulfonic acid (69,70). Since the by-product in this case would be the salt of pyridine and p-toluenesulfonic acid, there would be no opportunity for the formation of the 1-chloro-1-deoxy compounds.



Only three examples of the use of sulfonic acid anhydrides as reagents in carbohydrate chemistry were found in the literature at the time of this study. Rigby (71) claimed the p-toluenesulfonylation of alkali-treated cellulose using the acid anhydride but Bernoulli and Stauffer (72) were unable to repeat this work. Helferich and Gnutchel (67) methanesulfonylated methyl α-D-glucopyranoside utilizing methanesulfonic acid anhydride but did not describe an experimental procedure. Finally, and more recently, Jeanloz and Jeanloz (73) treated methyl 4,6-O-benzylidene-α-D-glucopyranoside with one mole of p-toluenesulfonic acid anhydride to isolate mainly a 2-O-p-toluenesulfonate.



EXPERIMENTAL

1. METHODS

1. Chromatography

(a) Paper chromatograms were developed on Whatman No. 1 paper using the solvent systems: (A) 1-butanol, pyridine, acetic acid, water (6:4:1:3 by vol.) and (B) the less dense phase of equilibrated 1-butanol, ethanol, water (5:1:4 by vol.) (74). The spray reagents utilized for compound detection were alkaline silver nitrate (75) and permanganate-periodate (76).

(b) Thin layer chromatograms (t.l.c.) were developed on Silica Gel G in a solvent which consisted of benzene and methanol (10:1 by vol.). Compounds were detected through the use of four spray techniques. Most useful was a sulfuric acid (ca. 25%) spray which was followed by heat treatment of the chromatogram. Permanganate-Periodate (76) found applicability mainly in the detection of glycals. A diphenylamine spray (ca. 5%) followed by observation of the chromatogram in U.V. light (77) specified the positions of *p*-toluenesulfonates. Finally, ferric hydroxamate (78) led to the specific identification of acetates.

(c) Column chromatography was one means of separation of otherwise intractable mixtures. Fractions, which were separated by a mechanical fraction collector, were examined mainly by optical rotation.

(i) Silicic acid columns were prepared by the method of Bredereck *et al* (79) and developed with various solvents.

(ii) Charcoal columns were prepared by the method of Whistler (80) and fractions were eluted by gradient elution with aqueous ethanol.

(iii) Microcrystalline cellulose columns were prepared by the method of Wolfrom (81). Fractions were eluted through the use of solvent (B) mentioned in connection with paper chromatography.

(d) Counter-current distribution was the second means to the separation of mixtures. In most cases, only four or five stages were utilized and therefore the separation was carried out by hand. Again, in most cases, the aqueous phase was held stationary and subjected to extraction by a moving organic phase.

2. Optical Rotations

These were measured through the use of a Perkin-Elmer Model 141 polarimeter.

3. Melting Points

Melting points were determined in capillary tubes with a Gallenkamp Melting Point Apparatus. They are uncorrected.

4. Spectroscopic Data

(a) Proton Magnetic resonance (n.m.r.) spectra were determined by the spectroscopic services group of this department using the appropriate Varian apparatus. Tetramethylsilane was used as the standard and all chemical shifts are tau (τ) values with respect to this standard.

(b) Infrared (i.r.) spectra were determined by the spectroscopic services group using a Perkin-Elmer 421 dual grating spectrometer.

11. REAGENTS

1. Solvents

(a) Ethanol and methanol were dried by established procedures (82).

(b) Commercial pyridine was dried by storage over potassium hydroxide.

(c) Commercial chloroform was purified, when it was necessary, by passage through a short column of alumina. This technique removed the ethanol stabilizer.

(d) Commercial N,N-dimethylformamide was dried over phosphorus pentaoxide and then distilled from sodium hydroxide and stored in the dark over Linde Molecular Sieves 3A.

(e) Commercial ethylene glycol was dried by fractional distillation at atmospheric pressure and then stored over Linde Molecular Sieves 3A.

2. Non-carbohydrate Reagents

(a) Magnesium amalgam was prepared by heating small pieces of magnesium, cleaned with diethyl ether, with mercury in vacuo at 105° according to the method of Berglund and Sillen (48). The solid amalgam has been claimed to have the formula Hg_2Mg (47) and therefore the metals were combined in this proportion. In most cases, the amalgam

was prepared in situ but, when prepared in advance, it was stored in vacuo.

(b) Anhydrous p-toluenesulfonic acid was handled, in every case, as a solution in N,N-dimethylformamide. These solutions were prepared by two methods. The first was a modification of a method reported by Morgan (58). The second and simpler method involved drying the solution of the acid by the use of 2,2-dimethoxypropane. The latter acted as a water scavenger under acidic conditions producing low boiling products which could be removed by de-gassing in vacuo. When necessary, acid strengths were determined by titration against standardized sodium hydroxide.

(c) p-Toluenesulfonic acid anhydride was synthesized by the method of Thunenberg (70) and recrystallized from a mixture of benzene and hexane, m.p. 129-132.5°; reported, 134-135° (83).

(d) Lead tetraacetate was available through the route of Bailar (84). The product was utilized without purification.

3. Carbohydrate Reagents

(a) Tetra-O-acetyl-α-D-glucopyranosyl bromide (II) was prepared by the method of Lemieux (85). The physical constants, m.p. 88.5-90.5, $[\alpha]_D + 195.5^\circ$ (c, 2.4 in chloroform)

were in good agreement with those reported by Lemiuex: m.p. 88-89°, $[\alpha]_D$ + 198° (c, 2 in chloroform).

(b) Tetra-O-acetyl-α-D-mannopyranosyl bromide (III) was prepared by the standard method (85) but was not obtained in a crystalline state. The n.m.r. spectrum in deuteriochloroform (Fig. 1) showed the following chemical shifts (τ value): H_1 (doublet), 3.68; H_2 (quartet), 4.56; H_3 (quartet), 4.25; H4, 4.64; $H_{5,6,6'}$, 5.6-6.1; acetyl (four signals), 7.8-8.1. The coupling constants (Hz) were: $J_{1,2'}$ 1.5; $J_{2,3'}$ 3.0; $J_{3,4'}$ 10.0.

(c) Tetra-O-acetyl-α-D-galactopyranosyl bromide (XIX) was prepared by the standard method (85). The n.m.r. spectrum of this compound in deuteriochloroform (Fig. 2) was identical to that reported by Horton and Turner (98).

(d) Penta-O-acetyl-α-D-altropyranose (XX) was prepared by the method of Richtmyer and Hudson (86). The physical constants, m.p. 121-122°, $[\alpha]_D$ + 61.5° (chloroform), compared well with those reported, m.p. 118-119°, $[\alpha]_D$ + 63.0° (C,5.0 in chloroform).

(e) Tetra-O-acetyl-α-D-gulopyranosyl bromide (XLI) was prepared by the treatment of mixed anomeric penta-O-acetyl-D-gulopyranose with hydrogen bromide in acetic acid. The material was isolated as a syrup and was utilized in this state. The n.m.r. spectrum in deuteriochloroform is shown in Fig. 24.

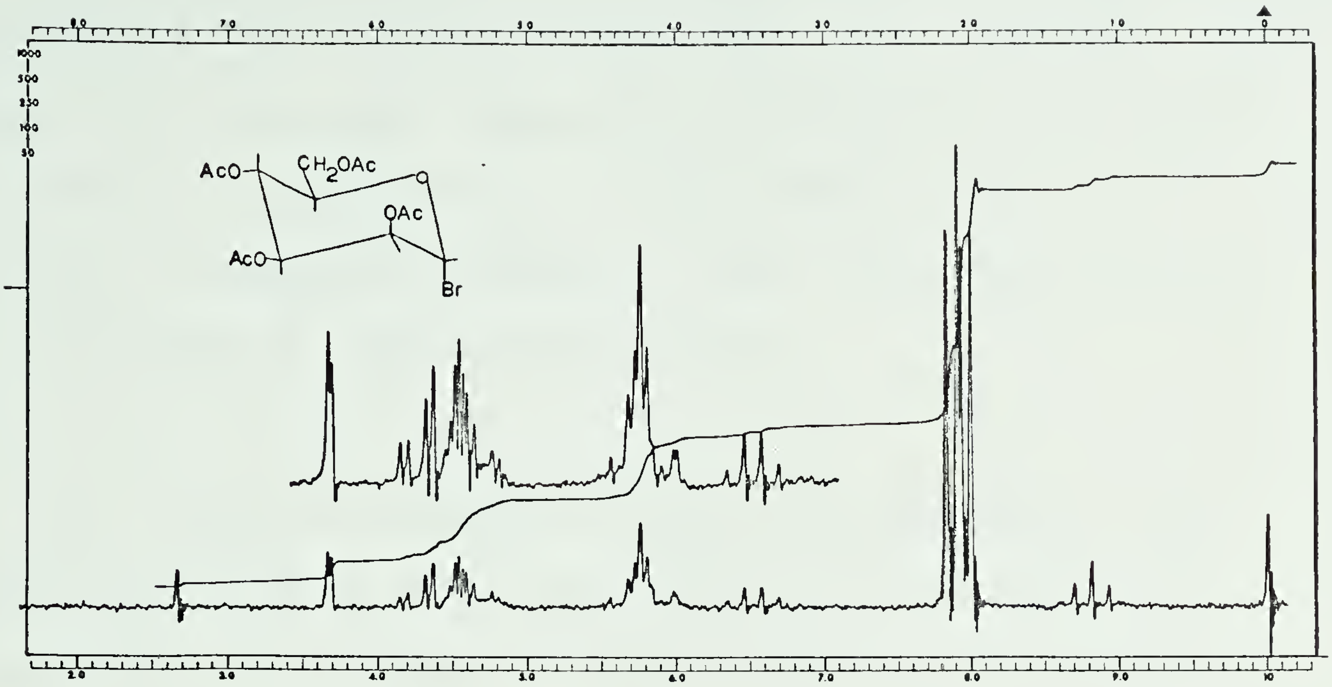


FIG. 1. N.m.r. spectrum (60 MHz) of tetra-O-acetyl-α-D-mannopyranosyl bromide (III) (deuteriochloroform

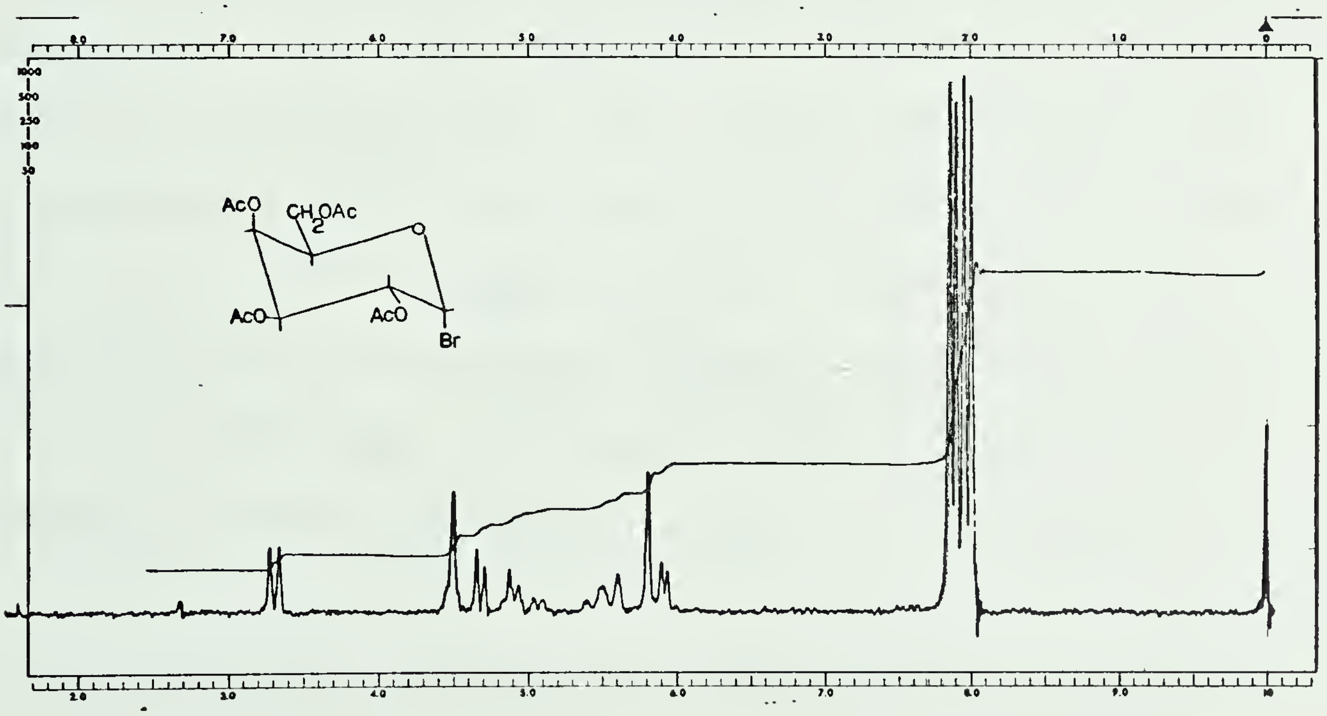


FIG. 2. N.m.r. spectrum (60 MHz) of tetra-O-acetyl-α-D-galactopyranosyl bromide (XIX) (deuteriochloroform)

(f) Tri-O-acetyl-β-L-arabinopyranosyl bromide (XXI) was prepared by the standard method (85), m.p. 139-141°. This agreed well with that reported by Gehrke and Aicher (22) for the β-D- configuration of the compound, m.p. 139°. The n.m.r. spectrum is shown in Fig. 3 and was observed on a solution in deuteriochloroform.

(g) Hepta-O-acetyl-α-maltosyl bromide (XXII) was synthesized from maltose octa-acetate by the method of Brauns (87). The material was obtained in an amorphous state, $[\alpha]_D$ + 180° (chloroform); reported, $[\alpha]_D$ + 180.26 (chloroform).

(h) Tri-O-acetyl-1,2-O-(1-exo-ethoxyethylidene)-α-D-glucopyranose (XVI) was prepared by a variation of the method of Lemieux and Morgan (6). The reaction was carried out at room temperature in chloroform with added 2,6-lutidine rather than at 50° in sym-collidine. The product was recrystallized from anhydrous ethanol, m.p. 94-96°; reported, 97-97.5° (88). The n.m.r. spectrum in deuteriochloroform is shown in Fig. 4.

(i) 3,4,6-Tri-O-acetyl-β-D-glucopyranosyl chloride (XXIII) was prepared in a two step pathway from β-glucose pentaacetate as described by Lemieux and Howard (89) The

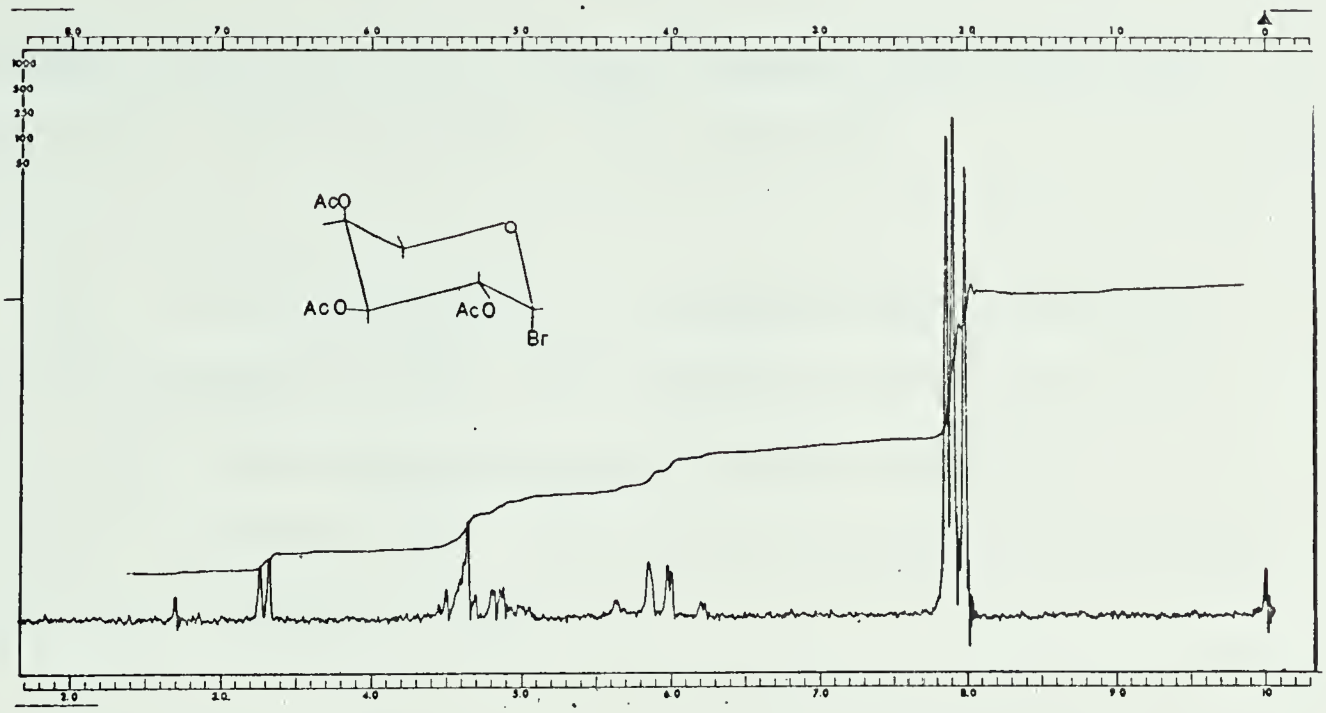


FIG. 3. N.m.r. spectrum (60 MHz) of tri-O-acetyl-β-L-arabinopyranosyl bromide (XXI) (deuteriochloroform)

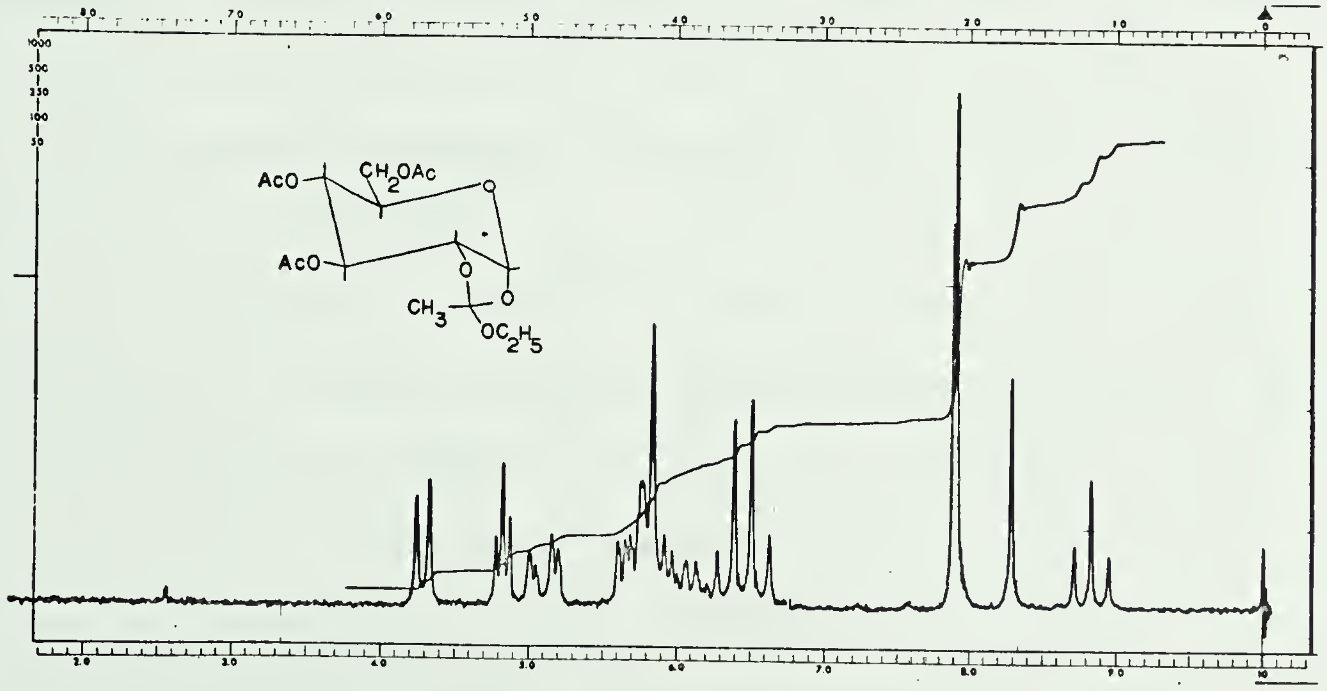


FIG. 4. N.m.r. spectrum (60 MHz) of tri-O-acetyl-1,2-O-(1-exo-ethoxyethylidene)-α-D-glucopyranose (XVI) (deuteriochloroform)

physical constant, m.p. 153-156° agreed well with that reported by these authors, m.p. 156-158°.

(j) Tri-O-acetyl-1,2-O-(1-exo-methoxyethylidene)-β-D-mannopyranose (XV11) was prepared by the method of Perlin (60) and recrystallized from hot methanol, m.p. 105-106°; reported 106°. The n.m.r. spectrum in deuteriochloroform is shown in Fig. 5.

(k) 2-Hydroxyethyl tetra-O-acetyl-β-D-glucopyranoside (XX1V) was prepared from tetra-O-acetyl-α-D-glucopyranosyl bromide (II) by the method of Karjala and Link (90). The product was recrystallized from water and the physical constants, m.p. 103.5-104.5°, $[\alpha]_D$ -26.4° (c, 4.8 in water) compared favourably with those previously reported, m.p. 105-106°, $[\alpha]_D$ -26.3° (c,3.5 in water). The n.m.r. spectrum of (XXIV) is shown in Fig. 6. It was determined at 100 MHZ in deuteriochloroform and showed the following chemical shifts (τ value): H_1 (doublet), 5.47: H_2, H_4, 4.89 - 5.16; H_3 (triplet), 4.80; H_5 and four protons of the aglycon, 6.15 - 6.45; H_6, $H_{6'}$, 5.8 - 5.9; acetyl (four peaks), 7.92 - 8.05; hydroxyl, 7.4. The coupling constants (Hz) were: $J_{1,2}$, 7.8; $J_{2,3}$, 9.0; $J_{3,4}$, 9.0 and $J_{4,5}$, 9.0.

(l) 2-Hydroxyethyl α-D-glucopyranoside (XXV) was

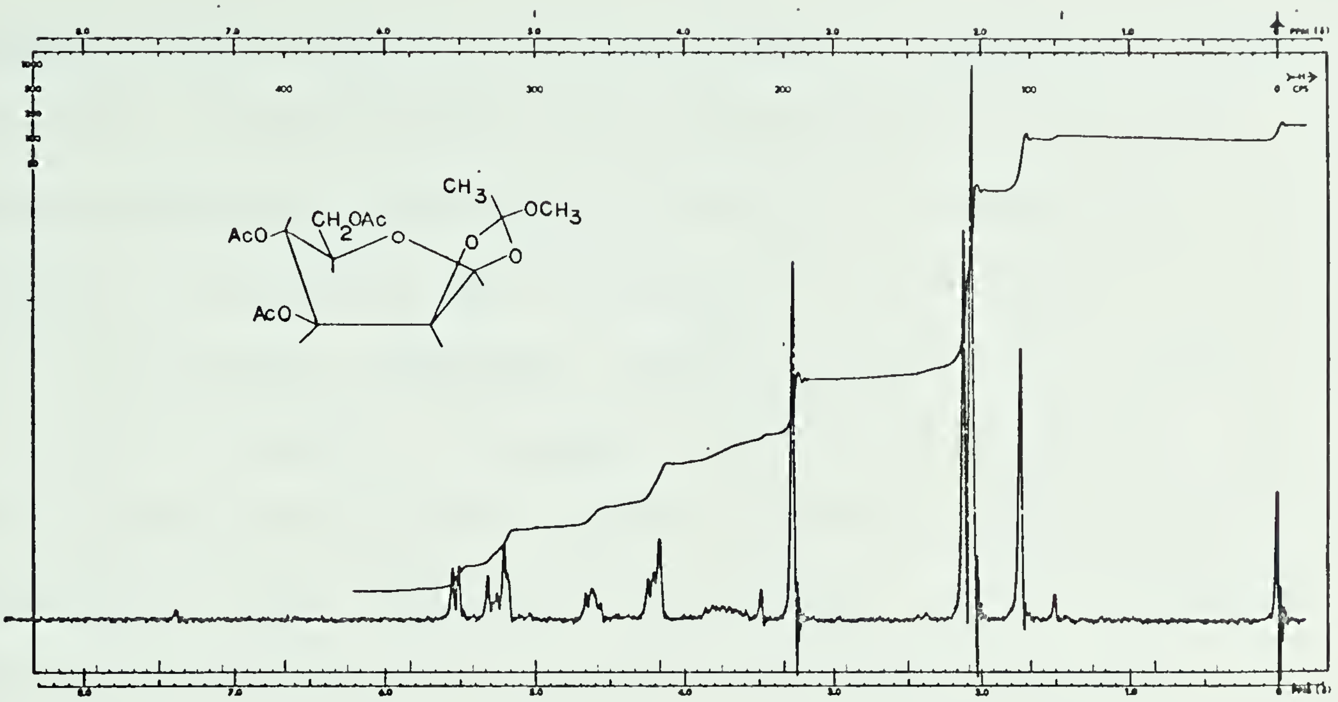


FIG. 5. N.m.r. spectrum (60 MHz) of tri-O-acetyl-1,2-O-(1-*exo*-methoxyethylidene)-β-D-mannopyranose (XVII) (deuteriochloroform)

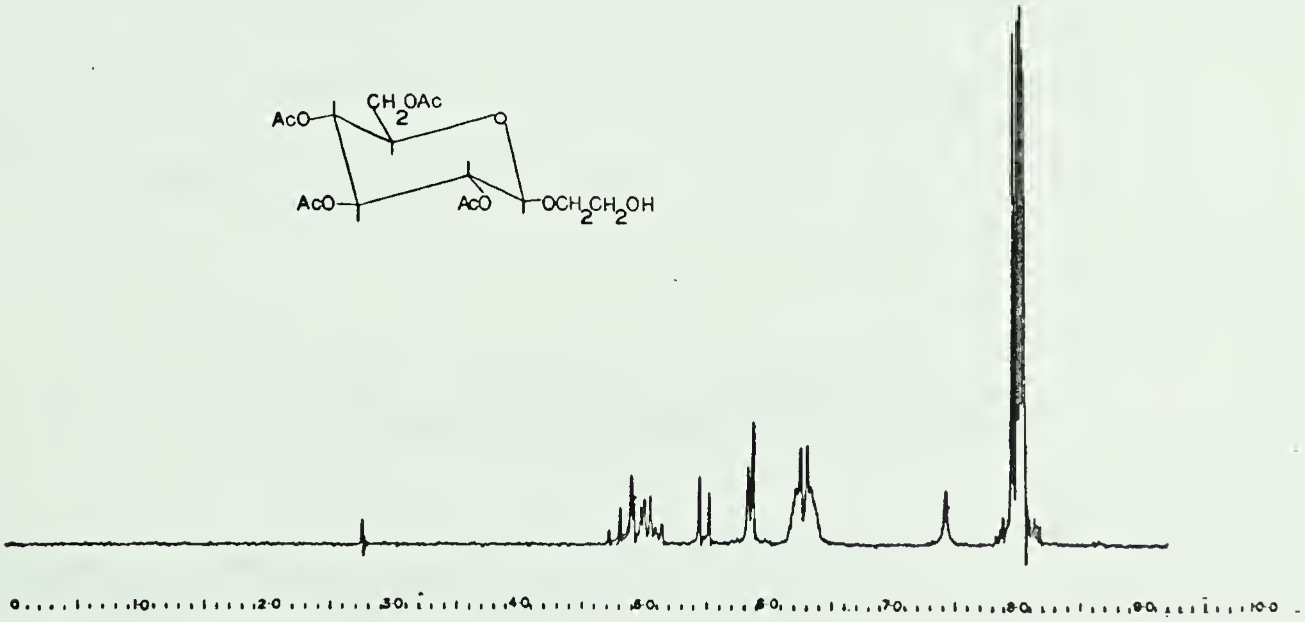


FIG. 6. N.m.r. spectrum (100 MHz) of 2-hydroxyethyl tetra-O-acetyl-β-D-glucopyranose (XXIV) (deuteriochloroform)

prepared from D-glucose by the method of Janson and Lindberg (91). The material was recrystallized twice from acetone with the addition of ethanol to solution and hexane to turbidity, m.p. 98.5-99.5° $[\alpha]_D$ + 134.8° (c, 0.6 in water; reported, 100-102° (92), $[\alpha]_D$ + 139° (c, 0.05 in water). A sample of XXV was acetylated through the use of equal amounts of acetic anhydride and pyridine at room temperature overnight. After a standard work-up, the resulting syrup was chromatographically homogeneous (t.l.c.). The n.m.r. spectrum of this acetylated product (XXVI) (Fig. 7) in deuteriochloroform showed the following chemical shifts (τ value): H_1 (doublet), 4.89; H_2 (quartet), 5.19; H_3 (triplet), 4.55; H_4 (triplet), 4.98; H_5, H_6, $H_{6'}$, 5.65-5.10; four protons of aglycon, 6.15-6.45; acetyl, 7.90-8.05. The coupling constants (Hz) observed were: $J_{1,2}$, 3.75; $J_{2,3}$, 10.25; $J_{3,4}$, 9.5 and $J_{4,5}$, 9.5.

III. SYNTHETIC INVESTIGATION

1. Glycal Synthesis By Metallic Reduction

(a) Tri-O-acetyl-1,2-dideoxy-D-*arabino*-hex-1-enopyranose (tri-O-acetyl-D-glucal) (I).

(i) From tetra-O-acetyl-α-D-glucopyranosyl

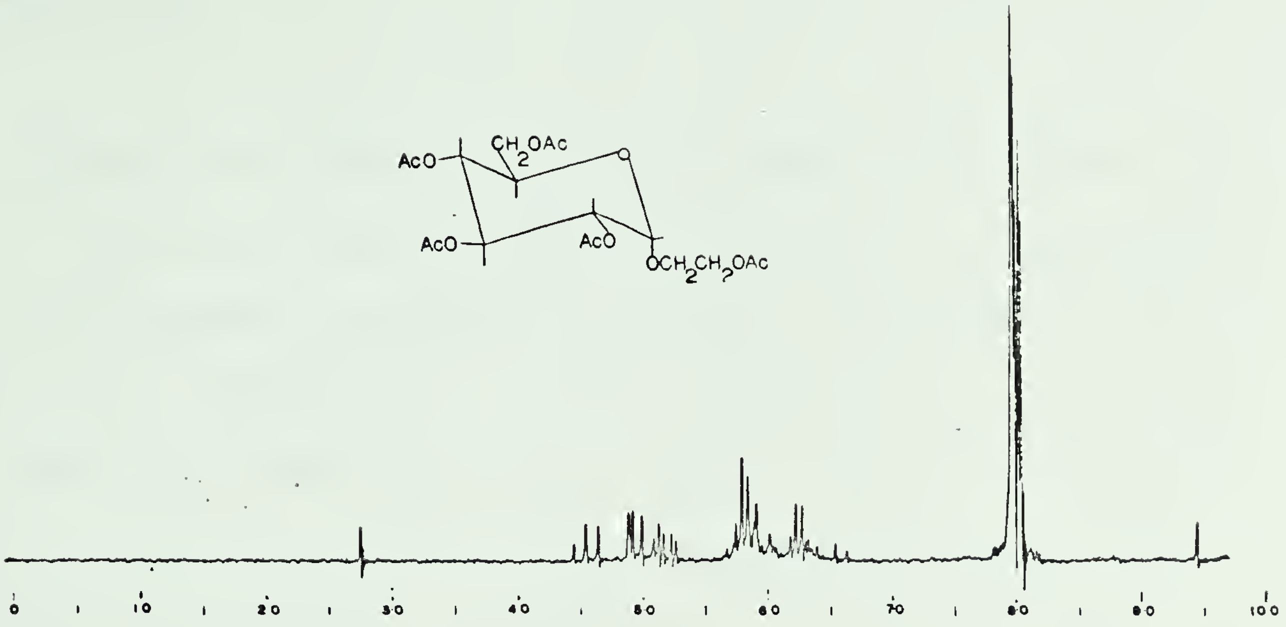


FIG. 7. N.m.r. spectrum (100 MHz) of 2-acetoxyethyl tetra-O-acetyl-α-D-glucopyranose (XXVI) (deuteriochloroform)

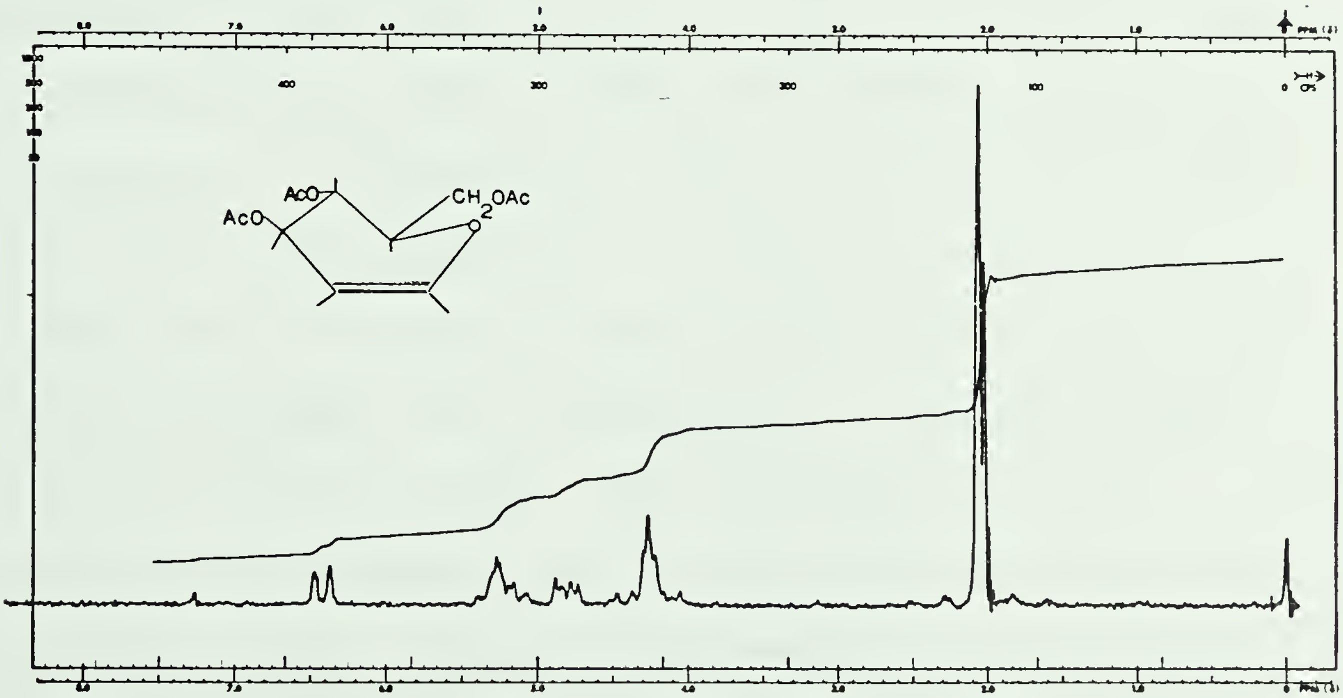


FIG. 8. N.m.r. spectrum (60 MHz) of tri-O-acetyl-1,2-dideoxy-D-arabino-hex-1-enopyranose (I) (deuteriochloroform)

bromide (II).

Magnesium ribbon, 1.44 g (59 mmole) was broken into small pieces and washed with diethyl ether. The material was dried under a stream of nitrogen and added to 23.6 g of mercury contained in a flask equipped for evacuation. The flask was evacuated, (0.1 mm Hg), sealed and heated at 100° for two hours. A solid magnesium amalgam was produced on cooling. A solution of tetra-O-acetyl-α-D-glucopyranosyl bromide (II), 6.00 g (14.6 mmole) in 13 ml of DMF, was de-gassed *in vacuo* and then added to the amalgam at atmospheric pressure. The reaction vessel was evacuated as before and sealed. It was agitated for one hour at room temperature. After the reaction flask had been returned to atmospheric pressure, the organic layer of the mixture was decanted into 200 ml of diethyl ether. The ether solution was filtered and the filtrate was concentrated *in vacuo* with the addition of xylene for the azeotropic removal of DMF. The resulting syrup was dissolved in chloroform and the chloroform solution was washed with water. After having been dried over sodium sulfate, the solution was concentrated *in vacuo* to a syrup which spontaneously crystallized. Tri-O-acetyl-1,2-dideoxy-D-*arabino*-hex-1-enopyranose (I) was identified by its n.m.r spectrum (Fig. 8) determined in deuteriochloroform. The product had formed in 98% yield, 3.9 g (14.3 mmole).

It was recrystallized twice from methanol and water, m.p. 54.5-56°; reported, 54-55° (12).

(ii) From tetra-O-acetyl-α-D-mannopyranosyl bromide (III).

This reaction was carried out in identical fashion and on an identical scale to that described above in the reduction of acetylated glucopyranosyl bromide. Again the crude tri-O-acetyl-1,2-dideoxy-D-arabino-hex-1-enopyranose (I) spontaneously crystallized and was identified by its n.m.r. spectrum. It had formed in 89% yield, 3.53 g (13 mmole). The material was recrystallized from methanol and water, m.p. 53-54°; reported 54-56° (12).

(b) Tri-O-acetyl-1,2-dideoxy-D-lyxo-hex-1-enopyranose (tri-O-acetyl-D-galactal) (IV).

In a method identical to that described for the reduction of II, tetra-O-acetyl-α-D-galactopyranosyl bromide (XIX), 1.50 g (3.6 mmole) was treated with magnesium amalgam (ca. 7 g). After a work-up similar to that previously described, a yellow syrup was obtained. The n.m.r. spectrum of this syrup indicated relatively pure tri-O-acetyl-1,2-dideoxy-D-lyxo-hex-1-enopyranose (IV) which had formed in 94.5% yield, 0.935 g (3.5 mmole). A sample of the material

was distilled (ca. 140° and 0.07 mm Hg) and an n.m.r. spectrum (fig. 9) was observed in deuteriochloroform. This spectrum showed very high purity.

(c) Tri-O-acetyl-1,2-dideoxy-D-ribo-hex-1-enopyranose (tri-O-acetyl-D-allal) (VI).

(i) Tetra-O-acetyl-α-D-altropyranosyl bromide (XXVII).

Penta-O-acetyl-α-D-altropyranose (XX), 5.0 g (12.8 mmole) was dissolved in 12 ml of glacial acetic acid. A cooled (0°) solution of hydrogen bromide in acetic acid (10 ml of 30%) was added and the new solution was allowed to stand without cooling for 1/2 h. The reaction mixture was diluted with 25 ml of chloroform and poured onto ice contained in a separatory funnel. The organic layer was separated and further washed to neutrality with sodium bicarbonate solution. The purified chloroform solution was then dried and concentrated *in vacuo*. Tetra-O-acetyl-α-D-altropyranosyl bromide (XXVII) crystallized from the resulting syrup on standing. The material had formed in 80% yield, 4.2 g (10.2 mmole). The compound was recrystallized three times from diethyl ether, m.p. 109-111°, $[\alpha]_D$ + 142.3° (c, 0.77 in chloform). The n.m.r. spectrum determined in deuteriochloroform is shown in Fig. 10.

(ii) Tri-O-acetyl-1,2-dideoxy-D-ribo-hex-1-enopyranose (VI).

Tetra-O-acetyl-α-D-altropyranosyl bromide (XXVII), 0.500 g (1.21 mmole) was treated with 2.5 g of magnesium amalgam as previously described. The crude product was purified by passage through a 1.5 by 20 cm silicic acid column which was eluted by a mixture of benzene, methanol and 2,6-lutidine (100:10:1 by vol.). The purified product, which spontaneously crystallized, was isolated in 65.3% yield, 0.215 g (0.79 mmole). The material was recrystallized from diethyl ether, m.p. 82.5-84.5°, $[\alpha]_D$ + 316.0° (C, 0.68 in chloroform). The n.m.r. spectrum determined in deuteriochloroform is shown in Fig. 11.

Anal. Calcd. for $C_{12}H_{16}O_7$ (272.2): C, 52.93; H, 5.92. Found: C, 52.76; H, 5.83.

(d) Tri-O-acetyl-1,2-dideoxy-D-xylo-hex-1-enopyranose (V) (tri-O-acetyl-D-gulal).

In a fashion similar to that previously described, tetra-O-acetyl-α-D-gulopyranosyl bromide (XLI), 1.75 g (4.25 mmole) was reduced with 7.5 g of magnesium amalgam. The crude product spontaneously crystallized and its n.m.r. spectrum indicated a yield of 60%. The material was recrystallized from diethyl ether, m.p. 98.0-99.5°, $[\alpha]_D$ + 255° (c,1.4 in chloroform; reported (20), m.p. 97-98°, $[\alpha]_D$ + 248° (chloroform). The n.m.r. spectrum in deuteriochloroform is shown in Fig. 25.

(e) Di-O-acetyl-1,2-dideoxy-L-erythro-pent-1-enopyranose (di-O-acetyl-L-arabinal) (XXVIII).

Tri-O-acetyl-α-L-arabinopyranosyl bromide (XXI), 4.93 g (14.6 mmole) was reduced with ca. 25 g of magnesium amalgam in the manner previously described. Di-O-acetyl-1,2-dideoxy-L-erythro-pent-1-enopyranose (XXVIII) was isolated as a mobile liquid in 97.5% yield, 2.85 g (14.2 mmole). The n.m.r. spectrum of the crude product compared very favourably with that of a sample distilled at 140° and 0.03 mm Hg. The latter spectrum is shown in Fig. 12, and was observed in deuteriochloroform.

(f) 1,2-Dideoxy-4-O-(α-D-glucopyranosyl)-D-arabino-hex-1-enopyranose (maltal) (XXIX).

A solution of hepta-O-acetyl-α-maltosyl bromide (XXII), 2.55 g (3.7 mmole) in 4 ml of anhydrous DMF was treated with 10.0 g of magnesium amalgam in the previously described method. An i.r. spectrum was determined on the syrup resulting from a normal work-up. This spectrum was utilized for comparison with that of di-O-acetyl-1,2-dideoxy-4-O-(tetra-O-acetyl-α-D-glucopyranosyl)-D-arabino-hex-1-enopyranose (XV), the product of a classical zinc dust reduction of hepta-O-acetyl-α-D-maltosyl bromide (XXII) as mentioned below. The spectra were identical.

In order that purification might be carried out more readily, the syrup was de-acetylated. It was dissolved in 34 ml of chloroform and the solution was cooled to -10°. A

solution of sodium methoxide in anhydrous methanol, prepared by the addition of 0.28 g of sodium to 24 ml of methanol, was added to the cold chloroform solution and the mixture was stirred at 0° for 1 hour with protection from atmospheric moisture. The product was extracted into 50 ml of ice-water which was neutralized with 8.5 ml of Amberlite IR-120 (H+) ion exchange resin. The resin was removed by filtration and the filtrate was concentrated _in vacuo_. A paper chromatogram developed with solvent B showed only one spot. 1,2-Dideoxy-4-O-α-D-glucopyranosyl-D-_arabino_-hex-1-enopyranose (XXIX) was formed in 92% yield, 1.04 g (3.4 mmole). Since crystalline material was not obtained, the product was further purified on a 4 by 46 cm microcrystalline cellulose column which was eluted with solvent B. The n.m.r. spectrum (Fig. 13) of a deuterium oxide exchanged sample of the purified fraction (0.670 g) showed the expected pattern. Crystalline material was not available, $[\alpha]_D$ + 114.5° (C, 1.1 in water); reported (40) $[\alpha]_D$ + 1.16° (water).

(g) 3,6-Di-O-acetyl-1,2-dideoxy-4-O-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)-D-_arabino_-hex-1-enopyranose. (hexa-O-acetyl-maltal) (XXIX). A nearly exact repetition of the procedure described by Gakhokidze (40).

Hepta-O-acetyl-α-maltosyl bromide, 0.500 g (0.72 mmole) was dissolved in 20 ml of 50% aqueous acetic acid and the solution was cooled to -5°. Zinc dust, 1.2 g was added and the reaction mixture was stirred for two hours at the former temperature. At the end of this period, the solids were removed by filtration and washed well with 50% aqueous acetic acid. The combined filtrate was diluted with water and exhaustively extracted with chloroform. The chloroform solution was then washed to neutrality with aqueous sodium bicarbonate and dried by passage through a filter paper. The solution was concentrated *in vacuo* to a cloudy syrup, 0.413 g. This was dissolved in hot ethanol and the solids were removed by filtration. The filtrate was concentrated *in vacuo* to a clear, colourless syrup. An i.r. spectrum was determined and utilized for comparison with the hexa-O-acetyl-maltal produced above. The spectra were identical.

2. Synthesis of Tri-O-acetyl-D-glucal Via 3,4,6-Tri-O-acetyl-1,2-di-O-*p*-toluenesulfonyl-α-D-glucopyranose (XXXIV).

(a) Tri-O-acetyl-1,2-O-(1-*exo*-2'-hydroxyethoxy-ethylidene)-α-D-glucopyranose (XXX).

(i) From tetra-O-acetyl-α-D-glucopyranosyl bromide (II).

(A) MONO-ORTHOESTER (XXX)

Tetra-O-acetyl-α-D-glucopyranosyl bromide (II), 5.0 g (12.15 mmole) and sodium bromide, 0.40 g (3.8 mmole) were dissolved in 12.5 ml of anhydrous N,N-dimethylformamide. Anhydrous ethylene glycol, 0.68 ml (12.15 mmole) was added and the reaction mixture was allowed to stand at room temperature for 18 hours. After dilution with 125 ml of methylene chloride, the mixture was washed with 20 ml of saturated aqueous sodium bicarbonate in two portions and then with 10 ml of water. The organic solution was dried over sodium sulfate and concentrated *in vacuo* to thick syrup, 5.26 g. This was placed on a column of silicic acid (3.5 by 35 cm) which was eluted with a mixture of benzene, methanol and 2,6-lutidine (1000:10:1 by vol.). The separation was followed polarimetrically and two pure compounds were obtained. One of these was the monomer described here and the other was the compound described below. Tri-O-acetyl-1,2-O-(1-*exo*-2-hydroxyethoxyethylidene)-α-D-glucopyranose (XXX) was isolated in 26% yield, 1.26 g (3.2 mmole) as a syrup which slowly crystallized. The product was recrystallized from diethyl ether with the addition of hexane to turbidity; m.p. 101.5-104° $[\alpha]_D$ + 22.9° (c, 1.3 in methylene chloride). The n.m.r. spectrum, determined in deuteriochloroform , is shown in Fig. 14.

Anal. Calcd. for $C_{16}H_{24}O_{11}$ (392.2): C, 48.98; H, 6.17. Found: C, 49.05; H, 6.07.

(B) BIS-ORTHOESTER (XXXI)

The dimeric modification of tri-O-acetyl-1,2-O-(1-exo-2'-hydroxyethoxyethylidene)-α-D-glucopyranose (XXXI) was also isolated in the chromatographic separation previously described. It was obtained as a syrup in 35% yield, 1.54 g (4.2 mmole). The product slowly crystallized and was recrystallized from diethyl ether with the addition of hexane; m.p. 102-104°, $[\alpha]_D$ + 25.4° (c, 0.96 in methylene chloride). The n.m.r. spectrum in deuteriochloroform of the dimer differed from that of the monomer (Fig. 14) only in the relative signal strength for the protons of the 2-hydroxyethoxy function. The i.r. spectrum of XXXI showed no absorption in the region normal for hydroxyl stretch, whereas, the spectrum of the monomer contained this feature. A mixed m.p. of the monomer and dimer was observed, 80-90°.

Anal. Calcd. for $C_{30}H_{42}O_{20}$ (722.6): C, 49.86; H, 5.85. Found: C, 50.03; H, 5.98.

(ii) From tri-O-acetyl-1,2-O-(1-exo-ethoxyethylidene-α-D-glucopyranose (XVI) by transorthoesterification.

Tri-O-acetyl-1,2-O-(1-exo-ethoxyethylidene)-α-D-glucopyranose (XVI), 0.378 g (1 mmole) was dissolved in

5 ml of anhydrous N,N-dimethylformamide containing ethylene glycol, 0.11 ml (2 mmole). An anhydrous solution of *p*-toluenesulfonic acid in N,N-dimethylformamide (0.5 ml; 0.496 M) was added and the reaction mixture was allowed to stand for 20 hours at room temperature with protection from atmospheric moisture. At the end of this period, the mixture was diluted with 35 ml of cold chloroform and then washed with 40 ml of 0.0063 N aqueous sodium hydroxide in four portions. The neutralized chloroform solution was further washed with water (20 ml), dried over sodium sulfate and concentrated *in vacuo* to a colourless syrup, 0.388 g. This was placed on a 2 by 20 cm silicic acid column which was eluted with a mixture of benzene, methanol and 2,6-lutidine (1000:10:1 by vol.). The separation was followed polarimetrically. Monomeric tri-O-acetyl-1,2-O-(1-*exo*-2'-hydroxyethoxyethylidene)-α-D-glucopyranose (XXX) was isolated as a crystalline compound in 52% yield, 0.196 g (0.51 mmole). The material was recrystallized from diethyl ether, m.p. 101.5-105°. As a second component of the chromatographic separation, unreacted starting material was isolated in 28% yield, 0.104 g (0.28 mmole). This was recrystallized from absolute ethanol, m.p. 94-97.5°; reported, 97-97.5° (88). The final component in the separation was not obtained in a crystalline state but was identified by a comparative t.l.c. as dimeric

tri-O-acetyl-1,2-O-(1-exo-2-hydroxyethoxyethylidene)-α-D-glucopyranose (XXXI) which was isolated in 5.9% yield, 0.021 g (0.029 mmole).

(b) 3,4,6-Tri-O-acetyl-α-D-glucopyranose (XXXII).

(i) From tri-O-acetyl-1,2-O-(1-exo- ethoxyethylidene)-α-D-glucopyranose (XVI).

An anhydrous 0.25 m solution of p-toluenesulfonic acid in N,N-dimethylformamide (17.9 ml) was added to a mixture of 52 ml of N,N-dimethylformamide and 26 ml of ethylene glycol. The mixture was allowed to stand for half an hour at room temperature with protection from atmospheric moisture. After this time, the mixture was degassed *in vacuo* (0.1 mm Hg) until there was no further evolution of low boiling material. Tri-O-acetyl-1,2-O-(1-exo-ethoxyethylidene)-α-D-glucopyranose (XVI), 6.74 g (17.9 mmole) was added and the reaction mixture was stirred (magnetically) *in vacuo* (0.1 mm Hg) for 2 hours. After dilution with 630 ml of chloroform, the reaction mixture was washed with 45 ml of 0.1 N aqueous sodium hydroxide. The aqueous layer was back-extracted with 350 ml of chloroform and the chloroform solutions were combined. These were dried by passage through a filter paper and concentrated *in vacuo*. The resulting syrup was subjected to a four stage methylene chloride and water

extraction procedure which resulted in the separation of two compounds. 3,4,6-Tri-acetyl-α-D-glucopyranose (XXXII) was obtained in 77.5% yield, 4.242 g (13.8 mmole). The compound did not crystallize although crystalline material had been isolated previously (66). The n.m.r. spectrum (Fig. 15) observed in deuteriochloroform allowed a ready identification of the material.

Anal. Calcd. for $C_{12}H_{18}O_9$ (306.3): C, 47.06; H, 5.92. Found: C, 46.77; H, 6.58 (345).

The other compound isolated in the extractive separation was shown in a comparative t.l.c. to be a tetra-O-acetyl-D-glucopyranose which had formed in 15.7% yield, 0.99 g (2.8 mmole).

(ii) From tetra-O-acetyl-α-D-glucopyranosyl bromide (II).

Tetra-O-acetyl-α-D-glucopyranosyl bromide (II), 5,00 g (12.15 mmole) and sodium bromide, 0.39 g (3.8 mmole) were dissolved in 12.5 ml of anhydrous N,N-dimethylformamide. Anhydrous 2,6-lutidine, 1.4 ml (12.15 mmole) and anhydrous ethylene glycol, 0.68 ml (12.15 mmole) were added and the reaction mixture was allowed to stand for 17 hours with protection from moisture.

In a separate flask, *p*-toluenesulfonic acid, 0.583 g (0.31 mmole) was treated *in vacuo* (0.1 mm Hg) at 130°

for 20 minutes. The resulting syrup was cooled and dissolved in 25 ml of N,N-dimethylformamide at atmospheric pressure. 2,2-Dimethoxypropane was added to the mixture which was then protected from moisture and allowed to stand for a half hour. The mixture was de-gassed in vacuo as before to remove all low-boiling material. The reaction flask was returned to atmospheric pressure with protection from moisture. Anhydrous ethylene glycol (17.5 ml) was added.

The former solution was decanted into the latter leaving the precipitate (2,6-lutidine hydrobromide) behind. The new mixture was stirred (magnetically) in vacuo (0.1 mm Hg) for 3 hours. After dilution with 300 ml of chloroform containing 0.3 ml of 2,6-lutidine, the reaction mixture was washed with 31 ml of 0.1 N aqueous sodium hydroxide. The aqueous layer was back-extracted with 150 ml of chloroform. The combined chloroform solutions were dried by passage through a filter paper and concentrated in vacuo with the addition of 5 ml of toluene as for the azeotropic removal of glycol (93). The resulting syrup contained two components which were separated by the use of a methylene chloride and water extraction procedure. One was identified by a comparative t.l.c. and by its n.m.r. spectrum as 3,4,6-tri-O-acetyl-α-D-glucopyranose (XXXII) which was isolated in 60.5% yield, 2.24 g (7.3 mmole).

The other fraction was similarly identified as a tetra-O-acetyl-D-glucopyranose which had been isolated in 37% yield, 1.56 g (4.5 mmole).

(iii) From 3,4,6-tri-O-acetyl-β-D-glucopyranosyl chloride (XXIII). A repeat of the preparation of Brigl and Schinle (66).

A solution of 3,4,6-tri-O-acetyl-β-D-glucopyranosyl chloride (XXIII), 0.250 g (0.77 mmole) in 1.3 ml of anhydrous acetone was treated with 0.166 g of silver carbonate and 0.043 ml of water. The mixture was agitated at room temperature for 2 hours and then the silver salts were removed by filtration. The precipitate was washed well with acetone and the filtrate was concentrated *in vacuo* to a syrup. The n.m.r. spectrum of this syrup corresponded exactly to that of the title compound prepared in the orthoacetate exchange method. A similar exact comparison between the i.r. spectra was also observed. The compound did not crystallize but 3,4,6-tri-acetyl-α-D-glucopyranose (XXXII) was isolated in nearly quantitative yield, 0.235 g (0.77 mmole).

(iv) Analytical periodate oxidation of 3,4,6-tri-O-acetyl-α-D-glucopyranose (XXXII).

Compound (XXXII), 0.0995 g (0.33 mmole) was dissolved in sodium acetate buffer solution (pH 3.8, 23 ml) in a 50 ml volumetric flask. Sodium periodate solution (25 ml, 0.8 mmole), prepared by dissolving sodium periodate (3.424 g, 16 mmole) in sodium acetate buffer solution and adjusting the volume to 500 ml, was added to the volumetric flask and the volume was made up to 50 ml with sodium acetate buffer solution. At the same time, a blank solution was prepared omitting only compound XXXII. Both solutions were mixed well and stored in the dark at room temperature. The oxidation was followed by the removal of 5 ml aliquots which were added to a mixture of 10 ml of saturated aqueous sodium bicarbonate and 2 ml of 29% aqueous potassium iodide. After 15 min in the dark, these analytical solutions were titrated against 0.005 M aqueous sodium arsenite (94) for the determination of liberated iodine by the method of Mueller and Friedberger (95). The results are recorded in Table I and a plot of moles of periodate consumed against time of reaction given in Fig. 16.

TABLE 1

Oxidation of 3,4,6-tri-O-acetyl-α-D-glucopyranose (XXXII) with sodium periodate.

Time (min)	3.5	15	45	102	132	1114
Moles $NaIO_4$ consumed for each mole	0.40	0.71	0.81	0.95	0.95	1.17

(v) Preparative periodate oxidation of 3,4,6-tri-O-acetyl-α-D-glucopyranose (XXXII).

3,4,6-Tri-O-acetyl-α-D-glucopyranose (XXXII), 0.248 g (0.8 mmole) was disssolved in a solution of sodium periodate, 0.184 g (0.9 mmole) in 8 ml of water. The

reaction mixture was allowed to stand 20 min at room temperature and then exhaustively extracted with chloroform. The combined chloroform extracts were dried over sodium sulfate and concentrated _in vacuo_. The resulting syrup (0.207 g, 0.7 mmole) was shown by its n.m.r. spectrum to be composed mainly of 2,3,5-tri-O-acetyl-D-arabinofuranose with some minor amounts of 2,3,5-tri-O-acetyl-4-formyl-aldehydo-arabinose. The mixture was saponified with 5 ml of a solution of 5% triethylamine in 50% aqueous methanol over a period of 24 hours. After neutralization with 2 ml of Amberlite MB-1 mixed bed ion exchange resin, the solution was filtered and concentrated _in vacuo_. A paper chromatogram developed in solvent A and containing comparative authentic samples of D-glucose and D-arabinose allowed the identification of the product as D-arabinose (Rg 1.2) which contained very small amounts of D-glucose. The syrup eventually crystallized but because of the small amounts of material involved, recrystallization was impossible.

(c) 3,4,6-Tri-O-acetyl-2-O-_p_-toluenesulfonyl-α-D-glucopyranosyl chloride (XXXIII).

3,4,6-Tri-O-acetyl-α-D-glucopyranose (XXXII), 0.0975 g (0.32 mmole) was dissolved in 0.5 ml of chloroform and treated with _p_-toluenesulfonyl chloride, 0.124 g (0.65

mmole) and pyridine, 0.06 ml (0.75 mmole). After 48 hours at room temperature, the reaction solution was diluted with 5 ml of chloroform and washed successively with aqueous bicarbonate and with water. The chloroform solution was dried over sodium sulfate and then concentrated in vacuo. The n.m.r. spectrum (Fig. 17) in deuteriochloroform indicated 3,4,6-tri-O-acetyl-2-O-p-toluenesulfonyl-α-D-glucopyranosyl chloride had been isolated in 80.5% yield, 0.123 g (0.26 mmole). A small sample of the syrup dissolved in a very dilute solution of nitric acid was treated with silver nitrate solution and a copious precipitate resulted. This positive chloride test served to further identify the compound which was not subjected to further work-up.

(d) 3,4,6-Tri-O-acetyl-1,2-di-O-p-toluenesulfonyl-α-D-glucopyranose (XXXIV).

3,4,6-Tri-O-acetyl-α-D-glucopyranose (XXXII), 0.306 g (1 mmole) was dissolved in 2 ml of alumina purified chloroform containing 0.24 ml (3 mmole) of anhydrous pyridine. The solution was cooled to -10^0 and p-toluenesulfonic acid anhydride, 0.808 g (2.5 mmole) was added. The mixture was agitated to solution and allowed to stand at room temperature for 20 hours. After dilution with 5 ml of chloroform, the reaction solution was washed

successively with aqueous bicarbonate and with water. It was dried over sodium sulfate and concentrated *in vacuo* to yield a clear syrup, 0.611 g. A sample of the material was purified by silicic acid column chromatography using an eluant which consisted of ethyl acetate, Skelly B and 2,6-lutidine (10:10:1 by vol.). A purified sample was obtained but only about one third of the material was recovered because of the instability of the compound. The n.m.r. spectrum (Fig. 18) of this pure sample in deuteriochloroform was only marginally different from that of the crude sample. Thus, the yield could be calculated on the basis of the crude weight as 98%, 0.611 g (0.98 mmole). No crystalline material was obtained and because of the latent instability of compound XXXIV, useful physical constants were unavailable.

(e) Tri-o-acetyl-1,2-dideoxy-D-*arabino*-hex-1-enopyranose (tri-O-acetyl-D-glucal) (I).

Sodium iodide, 0.99 g and zinc dust, 0.27 g were dried *in vacuo* (0.1 mm Hg) at 100° for 1/2 hour. 3,4,6-tri-O-acetyl-1,2-di-O-*p*-toluenesulfonyl-α-D-glucopyranose (XXXIV), 0.212 g (0.34 mmole) was added to the cooled mixture in 5 ml of anhydrous N,N-dimethylformamide. The reaction mixture was stirred (magnetically) at 100° for

1.5 hours with protection from moisture, and then poured into 50 ml of chloroform. The resulting precipitate was removed by filtration and the filtrate was washed repeatedly with water and dried over sodium sulfate. It was concentrated *in vacuo* to a clear syrup whose n.m.r. spectrum identified it as tri-O-acetyl-1,2-dideoxy-D-*arabino*-hex-1-enopyranose (I) which had formed in 74.5% yield, 0.070 g (0.26 mmole). A portion of the material was subjected to a short path high vacuum distillation and an i.r. spectrum of the distillate coincided exactly with that of an authentic sample.

3. Synthesis of Tri-O-acetyl-D-glucal (I) via 3,4,6-Tri-O-acetyl-1,2-di-O-*p*-toluenesulfonyl-α-D-mannopyranose (XXXV).

(a) 3,4,6-Tri-O-acetyl-D-mannopyranose (XVIII)

(i) From tri-O-acetyl-1,2-O-(1-*exo*-methoxyethylidene-β-D-mannopyranose (XVII). A variation of the method of Perlin (65).

A solution of *p*-Toluenesulfonic acid monohydrate, 0.3805 g (2.0 mmole) and 2,2-dimethoxypropane, 0.25 ml in 4 ml of anhydrous N,N-dimethylformamide was allowed

to stand at room temperature for 1.5 hours. The solution was then de-gassed in vacuo to remove the low boiling fractions. Anhydrous methanol, 4 ml (100 mmole) was added and finally tri-O-acetyl-1,2-O-(1-exo-methoxyethylidene)-β-D-mannopyranose (XVII), 0.381 g (1.05 mmole). The mixture was agitated to solution, with protection from moisture, and when 7 min had passed, it was neutralized with 0.6 g of silver carbonate. The silver salts were removed by filtration and the filtrate was concentrated in vacuo. The resulting syrup was dissolved in 6 ml of chloroform which was again filtered and concentrated. A four stage methylene chloride and water extraction procedure was utilized to isolate the product. 3,4,6-Tri-O-acetyl-D-mannopyranose (XVIII) had formed in 72% yield, 0.2218 g (0.73 mmole). The n.m.r. spectrum of this material corresponded to that reported by Perlin (65) but was neither well resolved nor amenable to analysis. The syrup was dissolved in diethyl ether and eventually needle-like crystals were obtained, m.p. 95.5-96°; reported, 96-98° (65).

(ii) Analytical periodate oxidation of 3,4,6-tri-O-acetyl-D-mannopyranose (XVIII).

Compound XVIII, 0.0789 g (0.258 mmole) was dissolved in sodium acetate buffer solution (pH, 3.8, 23 ml) and subjected to an oxidation procedure as described previously for the corresponding glucose compound. The results are recorded in Table II and a plot of moles of periodate consumed against time of reaction is given in Fig. 19.

TABLE II

Oxidation of 3,4,6-tri-O-acetyl-D-mannopyranose (XVIII) with sodium periodate.

Time (min)	4	16	43	170	300	500
Moles $NaIO_4$ consumed for each mole	0.27	0.35	0.52	0.84	0.90	0.93

(iii) Preparative periodate oxidation of 3,4,6-tri-O-acetyl-D-mannopyranose (XVIII).

3,4,6-Tri-O-acetyl-D-mannopyranose (XVIII), 0.120 g (0.39 mmole) and sodium periodate, 0.163 g (0.76 mmole) were dissolved in 7.5 ml of water. The reaction solution was allowed to stand at room temperature for two hours and then exhaustively extracted with chloroform. The combined chloroform extracts were concentrated *in vacuo* to a syrup which was shown by its t.l.c. to be a mixture of two compounds. A four stage methylene chloride and water extraction procedure was utilized to isolate a pure sample of one of these. The n.m.r. spectrum of this compound indicated the structure to be 2,3,5-tri-O-acetyl-4-formyl-aldehydo-arabinose which was isolated in 36% yield, 0.0427 g (0.14 mmole). The remaining mixture was composed mainly of 2,3,5-tri-O-acetyl-D-arabinofuranose which accounted for a yield of 57% 0.0614 g (0.22 mmole). Both fractions were saponified by treatment with a solution of 5% triethylamine in 50% aqueous methanol. After deionization with Amberlite MB-1 ion exchange resin, both solutions were filtered and concentrated *in vacuo*. Both resulting syrups showed only the presence of arabinose (Rg 1.2) when examined on a paper chromatogram developed in solvent A and containing reference spots of D-glucose and D-arabinose.

(b) Tri-O-acetyl-1,2-di-O-*p*-toluenesulfonyl-α-D-mannopyranose (XXXV).

3,4,6-Tri-O-acetyl-D-mannopyranose (XVIII), 0.339 g (1.1 mmole) was dissolved in 1.9 ml of alumina purified chloroform containing 0.3 ml (4 mmole) of anhydrous pyridine. The solution was cooled to -10° and p-toluenesulfonic acid anhydride, 0.935 g (2.9 mmole) was added. After standing at room temperature for 17 hours, the reaction mixture was diluted with 17 ml of ice cold chloroform and washed successfully with saturated aqueous bicarbonate and with water. The purified chloroform solution was dried over sodium sulfate and concentrated *in vacuo*. The resultant syrup (0.569 g) was dissolved in deuteriochloroform and both an n.m.r. spectrum and a t.l.c. were observed. Tri-O-acetyl-1,2-di-O-p-toluenesulfonyl-D-mannopyranose (XXXV) had been isolated in a relatively pure state and, because of the previously noted instability of such compounds, no further purification or characterization was attempted.

(c) Tri-O-acetyl-1,2-dideoxy-D-*arabino*-hex-1-enopyranose (Tri-O-acetyl-D-glucal) (I).

A mixture of sodium iodide, 2.4 g (16.1 mmole) and zinc dust, 0.74 g (11.5 mmole) was dried at 105° *in vacuo* (0.1 mm Hg) for 2 hours. After these materials had been returned to room temperature and pressure, a solution of tri-O-acetyl-1,2-di-O-p-toluenesulfonyl-α-D-mannopyranose (XXXV), 0.569 g (0.93 mmole) in 13 ml of N,N-dimethylform-

amide was added. The reaction vessel containing the mixture was evacuated (0.1 mm Hg) and then sealed. After a period of one hour with agitation at 105°, the reaction mixture was cooled and poured into 50 ml of chloroform. The solids were removed by filtration and the filtrate was washed over sodium sulfate and concentrated *in vacuo* with the addition of xylene for azeotropic removal of N,N-dimethylformamide. The resulting syrup was identified by its n.m.r. spectrum as tri-O-acetyl-1,2-dideoxy-D-*arabino*-hex-1-enopyranose (I) which was isolated in 53% yield, 0.145 g (0.49 mmole). The product was distilled at 125° and 0.05 mm Hg and the distillate crystallized. It was recrystallized from diethyl ether with the addition of hexane, m.p. 53-54°; reported, 54-55° (12).

4. Synthesis of maltal (XXIX) via the acetylated 1,2-di-O-*p*-toluenesulfonyl compound.

(a) 3,6-Di-acetyl-4-O-(tetra-O-acetyl-α-D-glucopyranosyl)-1,2-O-(1-*exo*-2'-hydroxyethoxyethylidene)-α-D-glucopyranose (XXXVI).

Hepta-O-acetyl-α-maltosyl bromide (XXII) 4.2 g (6.0 mmole) and sodium bromide, 0.345 g (3.4 mmole) were dissolved in 12.5 ml of anhydrous N,N-dimethylformamide.

2,6-Lutidine, 1.3 ml and anhydrous ethylene glycol, 0.676 g (12.15 mmole) were added and the mixture was allowed to stand at room temperature for 48 hours with protection from atmospheric moisture. After it was diluted with 125 ml of chloroform, the reaction mixture was washed successively with saturated aqueous bicarbonate and with water. The purified chloroform solution was dried over sodium sulfate and concentrated *in vacuo*. The syrup which resulted was placed on a 3.5 by 35 cm silicic acid column which was eluted with a mixture of benzene, methanol and 2,6-lutidine (1000:20:1 by vol.). Two purified compounds were obtained. The n.m.r. spectra of these two compounds were identical except for the relative signal strength of the peaks due to the protons of the glycol function. The compounds exhibited different mobilities on a t.l.c. They were identified as the title compound (XXXVI) and the *bis*-orthoacetate (XXXVII). The monomer (XXXVI) crystallized spontaneously in 16.9% yield, 0.687 g (1.01 mmole). It was recrystallized from diethyl ether, m.p. 191-193.5°, $[\alpha]_D + 68.8^\circ$ (c, 0.7 in chloroform). The n.m.r. spectrum in deuteriochloroform is shown in Fig. 20.

Anal. Calcd. for $C_{28}H_{40}O_{19}$ (680.6): C, 49.41; H, 5.92. Found: C, 49.44; H, 5.84 (604).

The *bis*-orthoacetate (XXXVII) crystallized spontaneously in 80% yield, 2.98 g (2.4 mmole). Unfortunately.

it was found that each attempt at recrystallization led to isolation of the monomer (XXXVI), and therefore, the material was handled in a chromatographically pure but only semi-crystalline state.

Anal. Calcd. for $C_{52}H_{68}O_{37}$ (1237): C, 50.49; H, 5.54. Found: C, 50.57; H, 5.98.

(b) 3,6,2',3',4',6'-Hexa-O-acetylmaltose (XXXVIII).

(i) Preparation from hepta-O-acetyl-α-maltosyl bromide (XXII).

Hepta-O-acetyl-α-maltosyl bromide (XXII), 2.5 g (3.6 mmole) and anhydrous sodium bromide, 0.118 g (1.2 mmole) were dissolved in 5 ml anhydrous N,N-dimethylformamide. After the addition of anhydrous ethylene glycol, 0.21 ml (3.6 mmole) and 2,6-lutidine, 0.41 ml (3.6 mmole), the reaction mixture was allowed to stand at room temperature for 20 hours.

In a separate flask, 0.9 ml of a 1.01 M anhydrous solution of *p*-toluenesulfonic acid in N,N-dimethylformamide was diluted with 7.5 ml of N,N-dimethylformamide and 2.5 ml (93.5 mmole) of ethylene glycol. After one half hour, this solution was de-gassed *in vacuo* (0.1 mm Hg) for the removal of low boiling fractions.

The former solution was decanted into the latter leaving the precipitated 2,6-lutidine hydrobromide behind. The new solution was stirred (magnetically) in vacuo (0.1 mm Hg) for 4 hours. At the end of this period, the reaction mixture was returned to atmospheric pressure and diluted with 88 ml of a 1% solution of 2,6-lutidine in chloroform. The chloroform solution was then washed with 10.5 ml of 0.1 aqueous sodium hydroxide. The aqueous layer was back-extracted with 45 ml of chloroform and the chloroform extracts were combined. They were dried over sodium sulfate and concentrated in vacuo with the addition of small amounts of xylene. The resulting syrup was dissolved in ethanol and a crystalline product immediately separated. This was identified as compound XXXVIII and represented a 46.5% yield, 0.996 g (1.7 mmole). A t.l.c. indicated that the solution retained sizable portions of XXXVIII and thus it was concentrated in vacuo. The resulting syrup was subjected to a four stage diethyl ether and water extraction procedure. A further 10.8% yield, 0.228 g (0.4 mmole) of XXVIII was isolated. All of the material was recrystallized from ethanol to constant rotation. The n.m.r. spectrum (Fig. 21) of XXXVIII in deuteriochloroform indicated that the material contained 1/2 mole of ethanol of crystallization. It should be noted that the figures for the carbon and hydrogen analysis are

within experimental limits regardless of whether the ethanol is considered in the calculations, m.p. 129.5-132.5°; $[\alpha]_D$ + 102.4° (c, 2.6 in chloroform).

Anal. Calcd. for $C_{24}H_{34}O_{17}$ (594.5: C, 48.48; H, 5.76; and for $C_{24}H_{34}O_{17}.1/2C_2H_5OH$ (617.55): C, 48.62; H, 6.04. Found: C, 48.26; H, 6.13.

A second pure compound was obtained from the four stage extraction procedure. This was identified as 2,3, 6,2',3',4',6'-hepta-O-acetyl-β-maltose (XXXIX) which was isolated in 28.3% yield, 0.593 g (0.9 mmole). The purification and identification of this compound is described separately.

(ii) Analytical periodate oxidation of 3,6, 2',3',4',6'-hexa-O-acetylmaltose (XXXVIII).

Compound XXXVIII 0.156 g (0.26 mmole) was dissolved in sodium acetate buffer solution (pH 3.8, 23 ml) and subjected to an oxidation procedure as described for compund XXXII in section 2 (b) (iv). The results are recorded in Table III and a plot of moles of periodate consumed against time of reaction is given in Fig. 22.

TABLE III

Oxidation of 3,6,2',3',4',6'-hexa-O-acetylmaltose (XXXVIII) with sodium periodate.

Time (min)	4.5	16	46	96	160
Moles $NaIO_4$ consumed for each mole	0.63	0.78	0.90	0.96	1.06

(iii) Preparative periodate oxidation of 3,6,2',3',4',6'-hexa-O-acetylmaltose (XXXVIII).

Lead tetraacetate, 0.666 g (0.15 mmole) was added to a solution of 3,6,2',3',4',6'-hexa-O-acetylmaltose (XXXVIII), 0.107 g (0.18 mmole) in 10 ml of glacial acetic acid. The reaction solution was allowed to stand at room temperature for 12 hours at which time a starch iodide test was negative. The solution was concentrated *in vacuo* and the resulting syrup was triturated repeatedly with diethyl ether. The combined ether fractions were filtered and the filtrate was concentrated *in vacuo*. Deacetylation was effected through treatment in 2 ml of a solution of 5% triethylamine in 50% aqueous methanol. After 24 hours, the deacetylation solution was treated with 1/2 ml of Amberlite MB-1 ion exchange resin. The resin was removed by filtration and the filtrate was concentrated *in vacuo*. The resulting syrup was identified as 3-O-(α-D-glucopyranosyl)-D-arabinose by the use of a paper chromatogram developed with solvent A and containing comparative spots (Rg 0.62) of an authentic sample (96). The disaccharide was then hydrolyzed through the action of 10 ml of 0.5 N aqueous hydrochloride acid at 100^0 for 6 hours. A sample of the hydrolysate, which had been neutralized with 12 ml of Amberlite MB-1 ion exchange resin, was analyzed on a

paper chromatogram developed with solvent A and containing reference spots of glucose (Rg. 1.0) and arabinose (Rg 1.2). The hydrolysate contained two compounds, D-glucose and D-arabinose.

(c) 2,3,6,2',3',4',6'-Hepta-O-acetyl-β-maltose (XXXIX).

This compound was obtained as a by-product in the preparation of the corresponding hexa-acetyl compound (XXXVIII) as previously described. Compound XXXIX, which had formed in 28.3% yield, 0.593 g (0.9 mmole) in the synthesis from hepta-O-acetyl-α-maltosyl bromide, was recrystallized from ethanol, m.p. 181.5-184°; $[\alpha]_D$ + 84.5° (c, 1.4 in chloroform); reported, 182-183°; $[\alpha]_D$ + 70.5° (c, 0.92 in chloroform) (81). The n.m.r. spectrum is shown in Fig. 23 and was determined in deuteriochloroform.

Anal. Calcd. for $C_{26}H_{36}O_{18}$ (636): C, 49.05; H, 5.70. Found: C, 49.11; H, 5.77.

(d) Hexa-O-acetyl-1,2-di-O-p-toluenesulfonyl-α-maltose (XL).

3,6,2',3',4',6'-hexa-O-acetylmaltose, 0.300 g (0.51 mmole) was dissolved in 1.9 ml of alumina purified chloroform. After the addition of 0.16 ml (2.0 mmole) of anhydrous

pyridine, the solution was cooled to -10° and p-toluenesulfonic acid anhydride, 0.468 g (1.4 mmole) was added. The mixture was agitated to solution with cooling and then allowed to stand at room temperature for 72 hours with protection from moisture. After it had been diluted with chloroform, the reaction solution was washed successively with aqueous bicarbonate and with water. It was dried over sodium sulfate and concentrated *in vacuo*. The resulting syrup showed only a single spot on a t.l.c. The n.m.r. spectrum, although not well resolved, did show a well defined anomeric doublet at τ 3.99 with a $J_{1,2}$ of 3.9 Hz. The yield was essentially quantitative and because of its high instability, the compound was utilized without further purification.

(e) 1,2-Dideoxy-4-O-(α-D-glucopyranosyl)-D-*arabino*-hex-1-enopyranose (maltal) (XXIX).

A mixture of sodium iodide, 1.2 g (8.1 mmole) and zinc dust, 0.370 g (5.7 mmole) was dried *in vacuo* (0.1 mm Hg) at 105° for two hours. This material was cooled and returned to atmospheric pressure with protection from moisture. A solution of hexa-O-acetyl-1,2-di-O-p-toluenesulfonyl-α-maltose (XL), 0.460 g (0.51 mmole) in 8 ml of anhydrous N,N-dimethylformamide was added and the reaction

flask was again subjected to vacuum (0.1 mm Hg) and sealed. The reaction mixture was heated at 105° for two hours with agitation and then the cooled flask was returned to atmospheric pressure. The contents of the flask were poured onto 100 ml of chloroform and the resulting mixture was filtered to remove the solids. The filtrate was washed repeatedly with water, dried over sodium sulfate and concentrated *in vacuo* with the addition of xylene. The n.m.r. spectrum of the resultant syrup identified the product as hexa-O-acetyl-maltal (XV) which had been formed in 64.5% yield, 0.183 g (0.32 mmole).

The product was dissolved in 3 ml of chloroform and the solution was cooled to -10°. A solution of sodium metal, 0.024 g (1.1 mmole) in 2 ml of anhydrous methanol was added and the mixture was agitated at 0° for 1 hour. The product was extracted into 10 ml of ice water and the resulting aqueous solution was neutralized with ca. 1 ml of Amberlite IR-120 (H+) ion exchange resin. After the resin was removed by filtration, the solution was concentrated *in vacuo*. The product was purified on a 4 by 46 cm microcrystalline cellulose column which was eluted with solvent B. The resulting syrup was identified as 1,2-dideoxy-4-O-(α-D-glucopyranosyl)-D-*arabino*-hex-1-enopyranose by the use of a paper chromatogram developed in solvent B and containing a comparative spot of an authentic sample

[Section 1 (f)]. The yield in the saponification was essentially quantitative.

DISCUSSION

In this investigation of new synthetic routes to aldose-related 1,2-unsaturated sugars, the first approach was toward the improvement of the metallic reduction technique utilizing acetylated glycosyl bromides as starting materials. The previously mentioned difficulties of the zinc dust in acetic acid method were such that one hoped to increase the reactivity of the metal and to decrease the reactivity of the solvent.

Because of its well known history in organic chemistry, magnesium was chosen for investigation as a reducing agent. Amalgamated magnesium held special promise for this work because it provided, as discovered by Darzens (43, 44), a high reactivity. Indeed, the lack of usage of the amalgam in organic chemistry after this discovery was rather surprising when compared with the widespread application of magnesium metal in the Grignard reaction. In fact, during the course of this work, a report appeared which described the advantages of the amalgam in the preparation of the di-Grignard from methylene diiodide (46).

In contrast to some amalgam preparations, the dissolution of magnesium in mercury is not a violently exothermic process and, in fact, the application of heat has been found necessary for the formation of a homogeneous product (48). Vacuum technique has also been used to advantage since it allows for reaction between mercury vapour and magnesium metal and thereby overcomes the difficulty of bringing the metals, which differ so widely in specific gravity, into contact. The compound Hg_2Mg, utilized in this work, was advantageous in that, while it contained a high proportion of magnesium (5.7%) and was a solid at room temperature, it immediately became a liquid as the magnesium was removed by reaction.

Once formed, the amalgam was found to be sensitive to air with the formation of a black oxide. In this respect, it was somewhat less active than the common alkali metals and could be handled without undue precaution. In water, however, it disintegrated with a brisk effervescence and therefore, a protective atmosphere was necessary during extended periods of reaction.

The recent emergence of N,N-dimethylformamide (DMF) as a low-cost commercially available organic solvent led to its consideration for use in the metallic reduction technique. As mentioned in the introduction, it was found to be stable both toward the amalgam and toward acetylated glycosyl bromides and its relatively low vapour pressure allowed the use of vacuum technique for the prevention of atmospheric contamination.

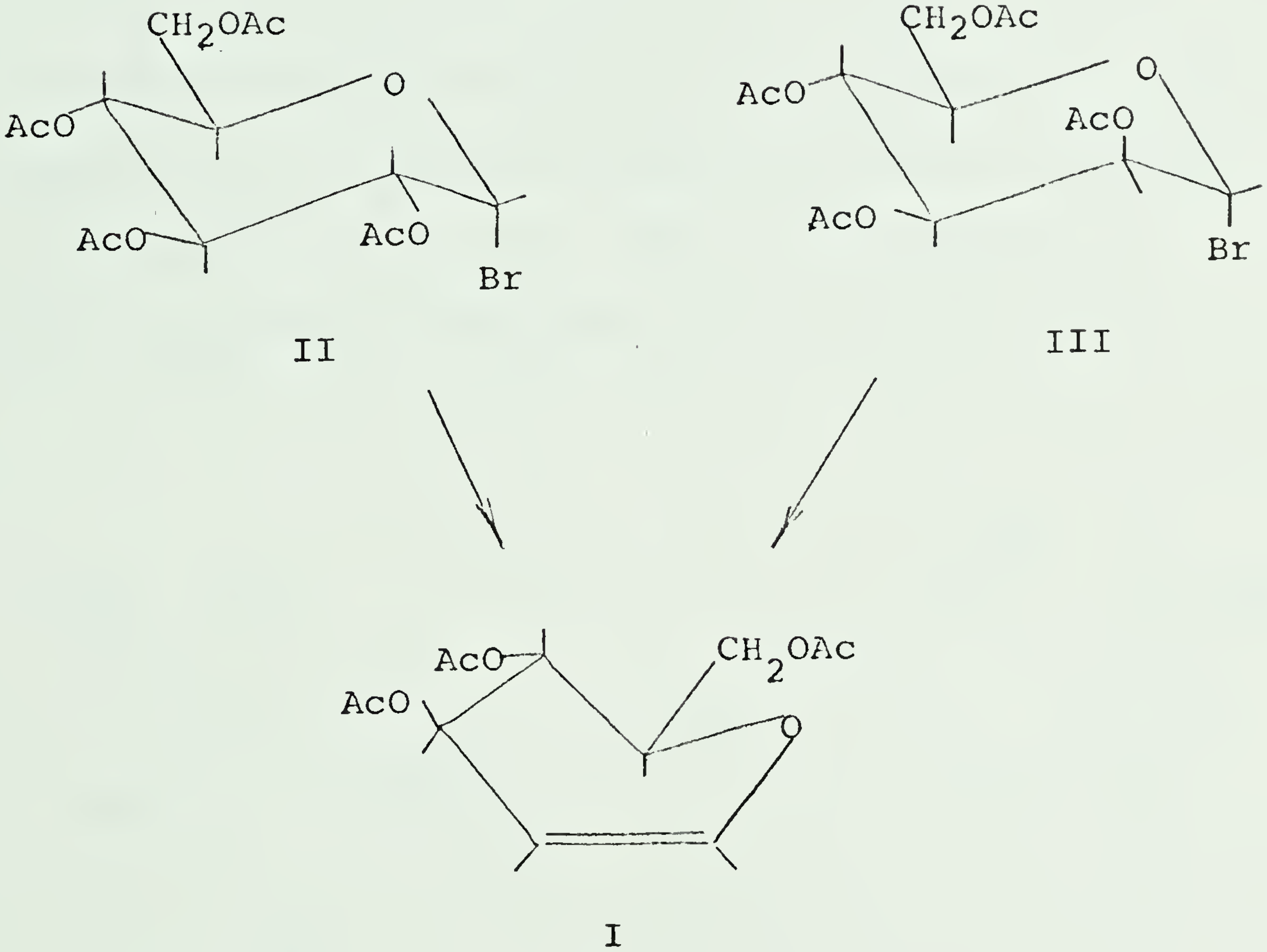
A series of small scale trial experiments concerning actual reductions were undertaken to ascertain the feasibility of the reaction. First of all, readily obtained tetra-O-acetyl-α-D-glucopyranosyl bromide (II) was treated on about 100 mg scale in DMF with an excess of pre-prepared amalgam. The occurrence of reaction was almost immediately apparent since, on agitation, the amalgam gradually liquified. The presence of the hoped for tri-O-acetyl-1,2-dideoxy-D-arabino-hex-1-enopyranose (I) in good yield was rapidly established by a t.l.c. A mere 15 minutes at room temperature seemed sufficient to render the reaction complete.

For work-up, it was necessary to remove only the mercury, the magnesium salts and the solvents. The mercury was easily left behind by decantation of the organic solution. The magnesium salts were precipitated with ether and removed by filtration. Finally, the DMF was removed

by azeotropic distillation with xylene. The i.r. spectra of syrups isolated in this fashion from small scale experiments were identical to the spectrum of an authentic sample of tri-O-acetyl-1,2-dideoxy-D-arabino-hex-1-enopyranose (I).

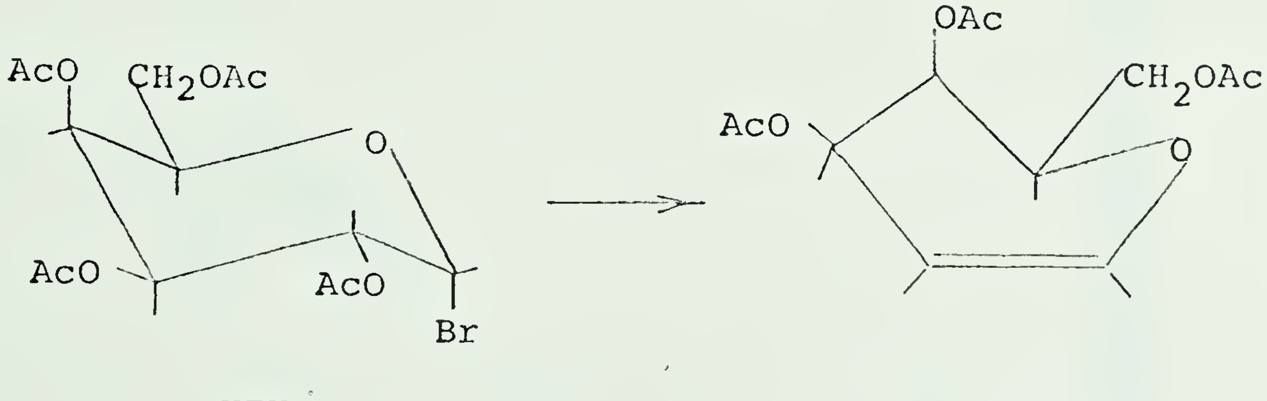
Consideration was then turned to the possibility of reduction of an acetylated glycopyranosyl chloride. This route to the synthesis of 1,2-unsaturated aldoses would have been preferred because of the greater stability of the chlorides ,but a small scale experiment attempted utilizing tetra-O-acetyl-β-D-glucopyranosyl chloride (XXIII) gave absolutely no indication of glycal formation. It seemed therefore that glycosyl chlorides lacked the necessary reactivity for the deacetoxyhalogenation reaction.

Of necessity then, attention was focused on preparative reductions of acetylated glycosyl bromides. On this larger scale, the best results were obtained when the amalgam was used in the ratio of four moles (based on Hg_2Mg) per mole of bromide and the reaction time was increased to about one hour. In the case of tetra-O-acetyl-α-D-glucopyranosyl bromide (II), the reduction led to a 98% yield of tri-O-acetyl-1,2-dideoxy-D-arabino-hex-1-enopyranose (I) which spontaneously crystallized.


CH$_2$OAc
AcO
O
AcO
AcO
Br
II
CH$_2$OAc
AcO
O
AcO
AcO
Br
III
AcO
AcO
CH$_2$OAc
O
I

Compound I was also formed by the reduction of tetra-O-acetyl-α-D-mannopyranosyl bromide (III) in 89% yield. Thus, the amalgam deacetoxyhalogenation was proven possible both with the 1,2-cis and the 1,2-trans orientations of the acetoxy and bromide functions. This, of course, was a primary requisite if the reaction was to find wide application in the carbohydrate field.

A second acetylated glycal in the aldohexose series was obtained by the amalgam reduction of tetra-O-acetyl-α-D-galactopyranosyl bromide (XIX) to tri-O-acetyl-1,2-dideoxy-D-lyxo-hex-1-enopyranose (IV) in 94.5% yield.



XIX IV

Compound IV did not crystallize and indeed, with a m.p. of 30°, has been obtained in a crystalline state only once (2). A purified sample was obtained by distillation and the n.m.r. spectrum (Fig. 9, Table V) of this sample was identical to that previously described by O'Neill (26).

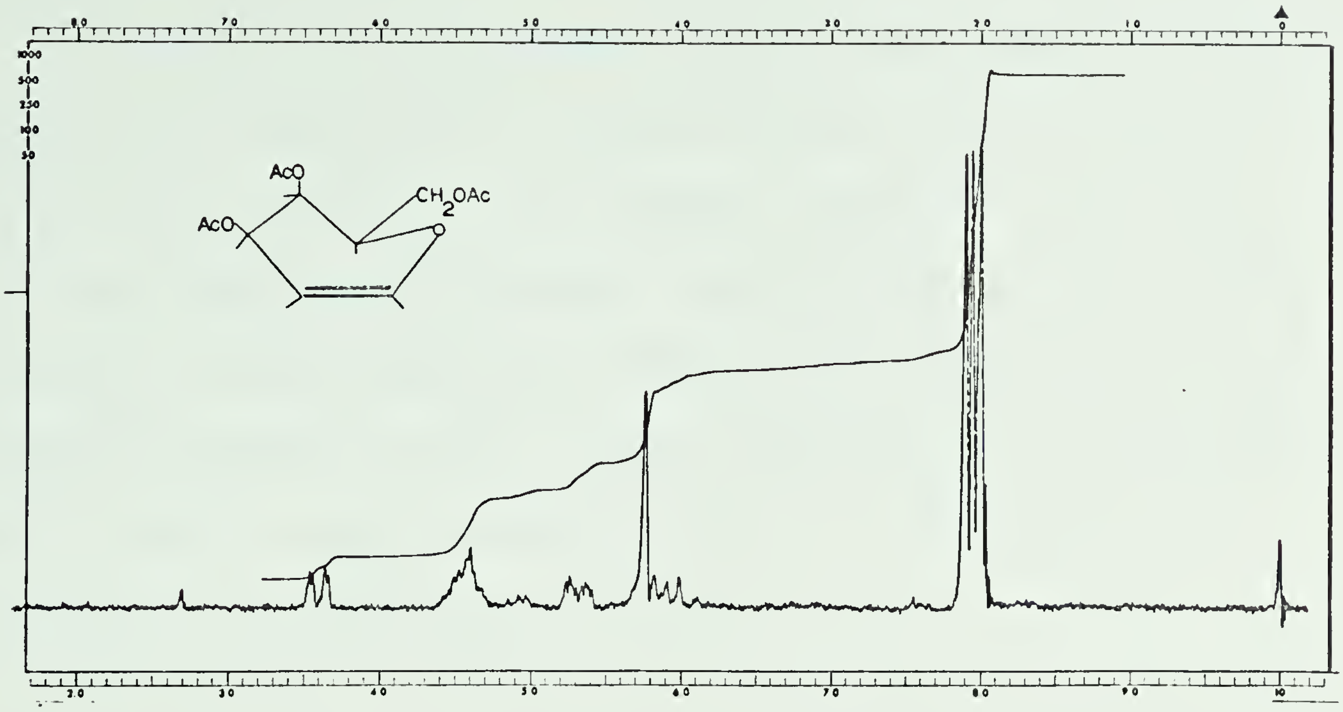


FIG. 9. N.m.r. spectrum (60 MHz) of tri-O-acetyl-1,2-dideoxy-D-lyxo-hex-1-enopyranose (IV) (deuteriochloroform)

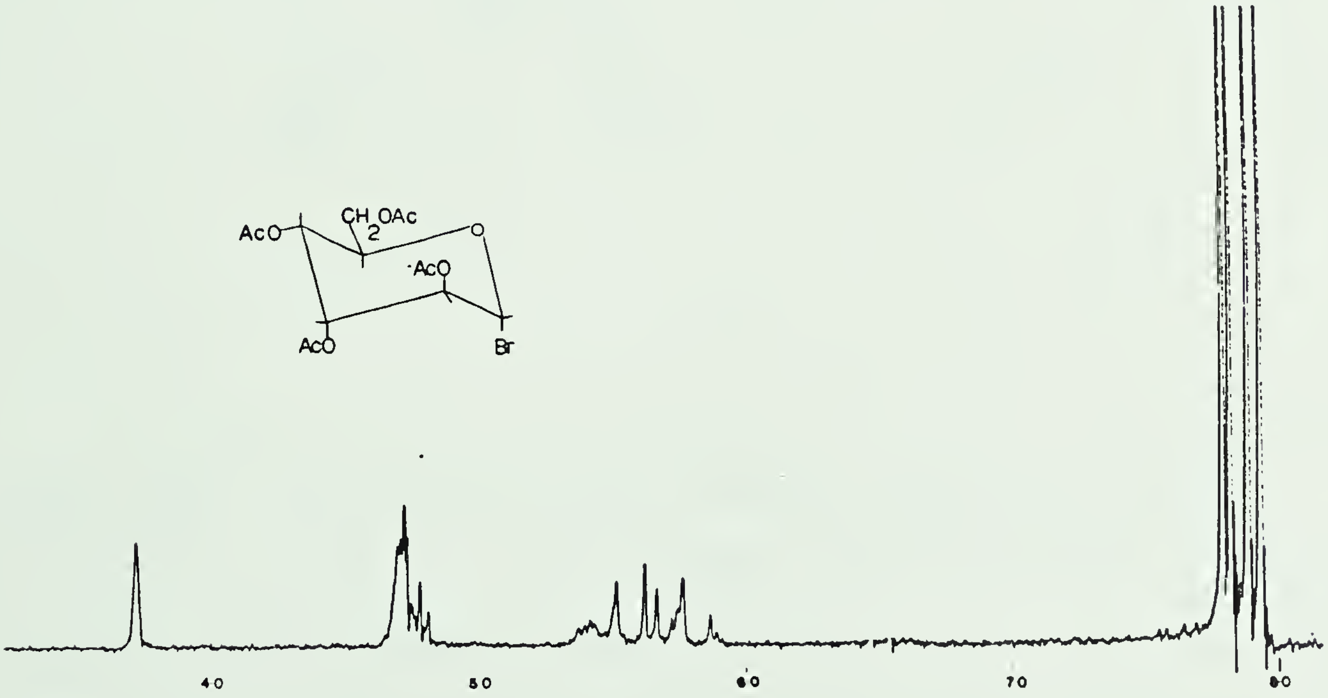
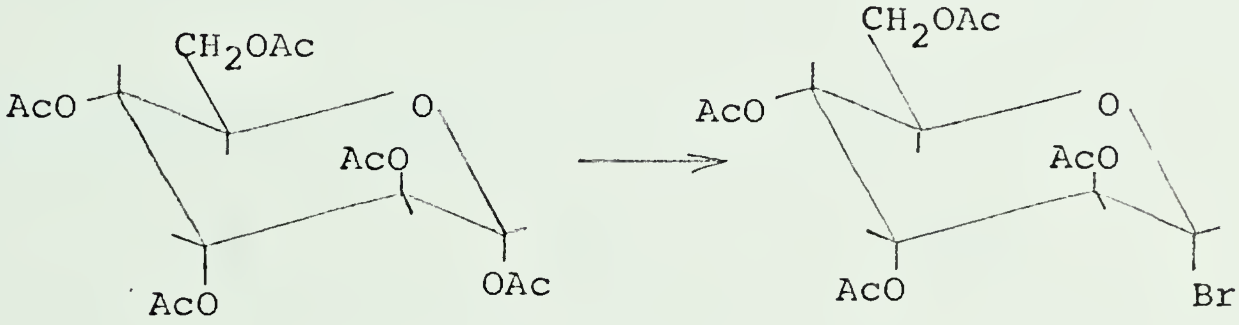


FIG. 10. N.m.r. spectrum (100 MHz) of tetra-O-acetyl-α-D-altropyranosyl bromide (XXVII) (deuteriochloroform)

A third 1,2-unsaturated hexopyranose was made available by the reduction of tetra-O-acetyl-α-D-altropyranosyl bromide (XXVII). This latter compound, which had not been reported previously, was synthesized from penta-O-acetyl-α-D-altropyranose (XX) by the action of hydrogen bromide in acetic acid. It was obtained in a crystalline state and its n.m.r. spectrum (Fig. 10, Table IV) was analysed for conformational data.



XX

XXVII

There were, of course, four limiting possibilities of molecular geometry. Two of these contained the α-configuration of the anomeric centre and two, the β-configuration. The 1C conformation of the α-bromide (XLII) could be immediately discounted on the basis of the anomeric signal of the n.m.r. spectrum. The Karplus relationship (100) would predict a large (7 - 10 Hz) coupling constant ($J_{1,2}$) for this conformation and the actual spectrum showed a coupling too small to be measured.

TABLE IV

N.m.r. parameters (100 MHz) of tetra-O-acetyl-α-D-altropyranosyl bromide (XXVII) in deuteriochloroform.

Chemical shifts, τ value

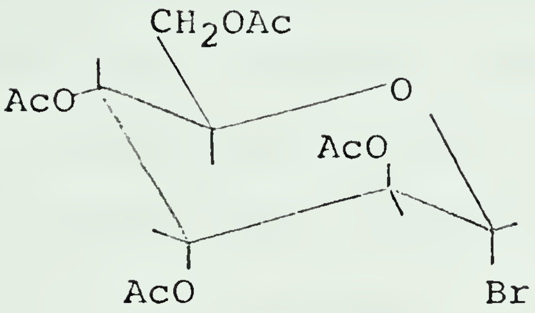
H_1	H_2, H_3, H_4	H_5
3.71	4.6-4.85	5.35-5.55

Chemical shifts, τ value

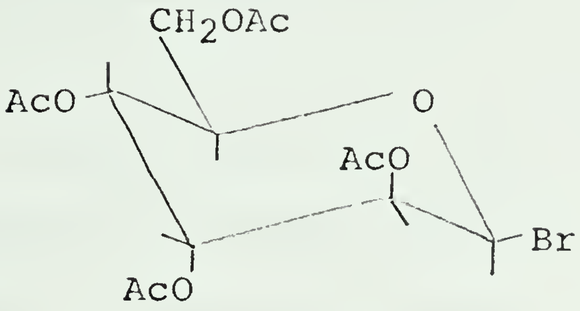
H_6	$H_{6'}$	Acetyl
5.61	5.81	7.78 7.81 7.92 7.87

Approximate coupling constants, Hz

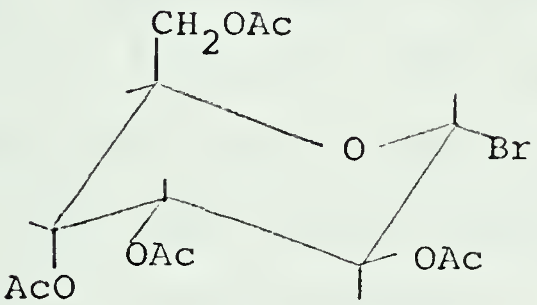
$J_{1,2}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
ca. 0	2.2	2.2	12.0


CH2OAc
AcO
O
AcO
AcO
Br

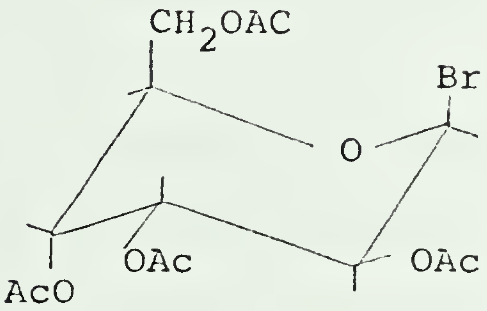
XXVII


CH2OAc
AcO
O
AcO
Br
AcO

XLIII


CH2OAc
O
Br
OAc
OAc
AcO

XLII


CH2OAC
Br
O
OAc
OAc
AcO

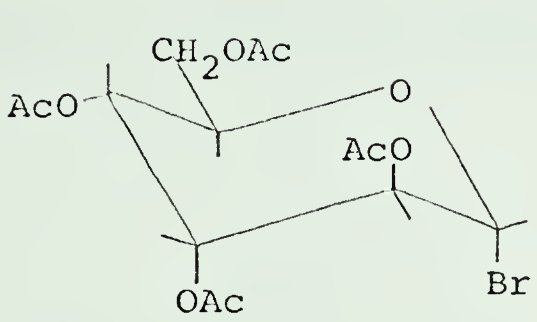
XLIV

This very small $J_{1,2}$ suggested a rather larger dihedral angle between H-1 and H-2 than shown in any of the remaining limiting possibilities. Such an effect would tend to rule out a conformation close to XLIV since an increase in the angle there would require the axial bromide to move toward the axial acetoxymethyl at C-5. In fact, the reverse effect would be expected if, indeed, a conformation with these two groups in opposition were possible.

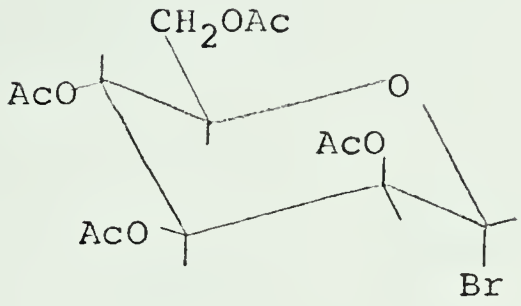
On the other hand, an increase in the dihedral angle between H-1 and H-2 would be expected in XXVII since this would relieve the interaction between the axial bromide and the axial 3-acetoxy group.

Two factors operated against XLIII. The first of these was the well recognized tendency of bromide substituents to assume an axial orientation. The second factor was the rather high positive observed rotation of the product. While Hudson's rules were not entirely satisfactory in this area, they could be used to calculate rotations for the two configurations of acetobromoaltrose using data from tetra-O-acetyl-α- and β-D-glucopyranosyl bromide and penta-O-acetyl-α and β-D-altropyranose. The calculated values for tetra-O-acetyl-α and β-D-altropyranosyl bromide were $+111^{\circ}$ and -87° respectively, and certainly the observed value ($+142.8^{\circ}$) was much closer to the calculated value for the α-product .

One final feature of the n.m.r. spectrum should be described: that is, the down-field shift of the doublet of multiplets due to H-5 as compared to the position of this signal in the spectrum (Fig. 1) of the manno compound (III). In XXVII or XLIII such an effect could be assigned to deshielding by the axial C-3 acetoxy as described in the rules elaborated by Lemieux and Stevens (101).

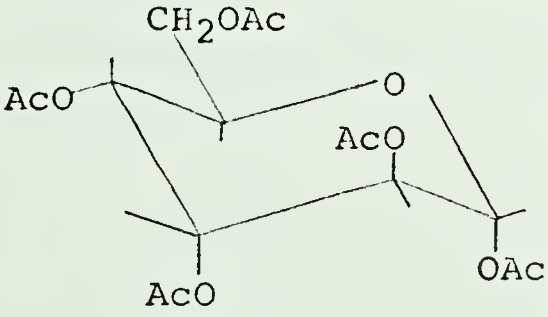


XXVII



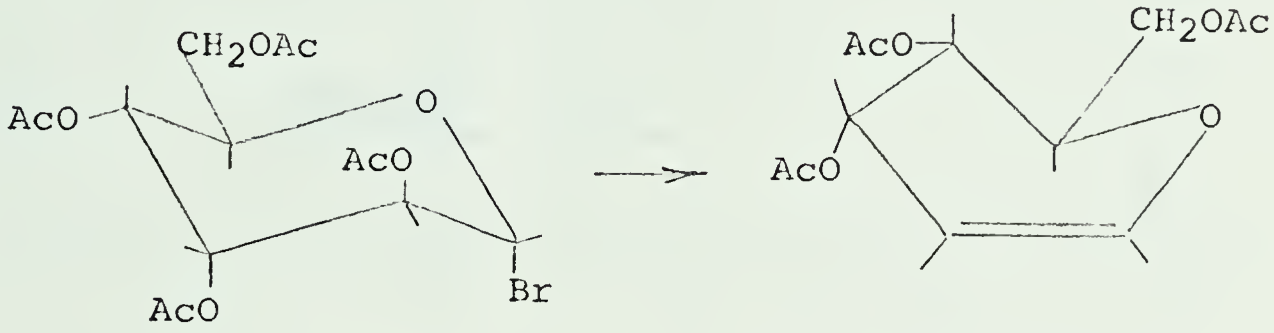
III

While the data did not allow an unequivocal assignment of the molecular geometry, the facts certainly point toward the configuration and conformation shown in XXVII. The n.m.r. spectrum was comparable to that reported by Coxon (99) for penta-O-acetyl-α-D-altrose (XX) in the C-1 conformation.



XX

A yield of 80% was achieved in the reduction of tetra-O-acetyl-α-D-altropyranosyl bromide (XXVII) to tri-O-acetyl-1,2-dideoxy-D-*ribo*-hex-1-enopyranose (VI).



XXVII VI

This acetylated 1,2-unsaturated sugar had not been reported previously although the corresponding 4,6-O-benzylidene compound was known (56). The n.m.r. spectrum (Fig. 11 , Table V) was analysed readily.

The relationships between coupling constants and dihedral angles elaborated by Karplus (100) and Garbisch (28) allowed the establishment of the conformation from this spectrum. The dependence of the allylic coupling constant $J_{1,3}$ upon the dihedral angle $\phi_{2,3}$ had been shown to be:

$$J_{1,3} = 3.9 \cos^2\phi - 2.6$$

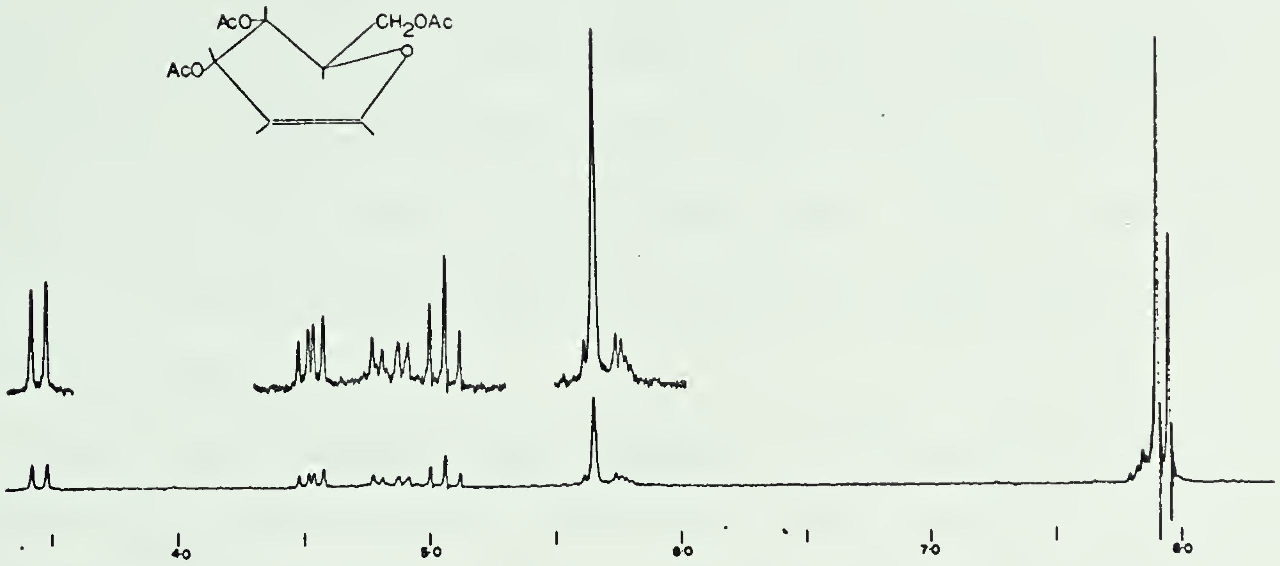


FIG. 11. N.m.r. spectrum (100 MHz) of tri-O-acetyl-1,2-dideoxy-D-*ribo*-hex-1-enopyranose (VI) (deuteriochloroform)

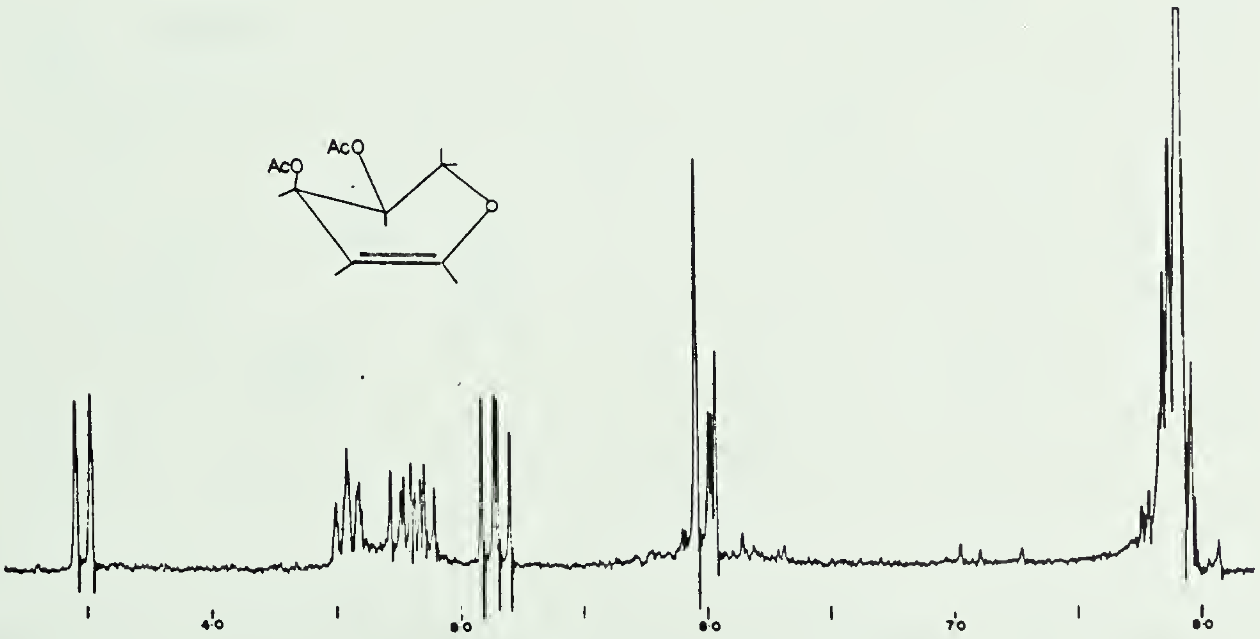
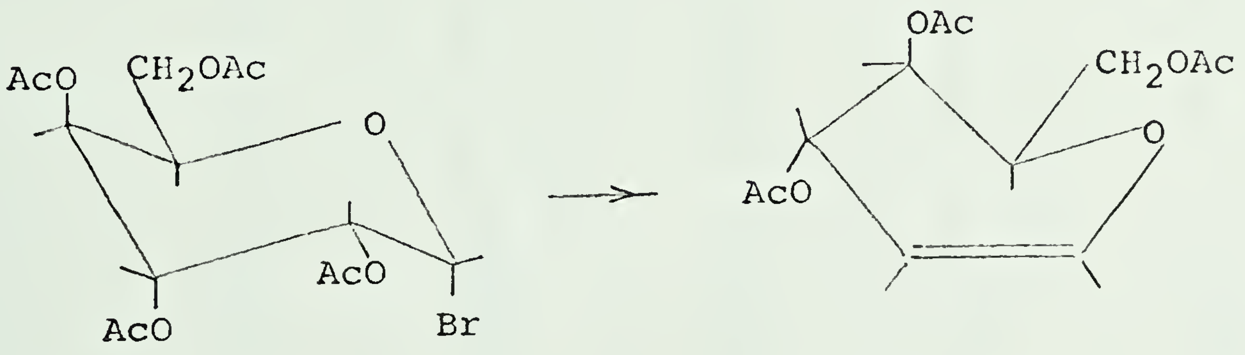


FIG. 12. N.m.r. spectrum (100 MHz) of di-O-acetyl-1,2-dideoxy-L-*erythro*-pent-1-enopyranose (XXVIII) (deuteriochloroform)

and thus, with a $J_{1,3}$ of ca. 0°, $\phi_{2,3}$ was expected to be close to 35°. This indicated that the C-3 acetoxy had assumed a nearly axial orientation. The dihedral angles $\phi_{3,4}$ and $\phi_{4,5}$ were assigned as ca. 45° and ca. 180° respectively on the basis of a Karplus type (100) dependence and these angles were compatible with the half-chair conformation shown.

The final hexopyranose glycal, tri-O-acetyl-1,2-dideoxy-D-xylo-hex-1-enopyranose (V), was prepared by the deacetoxyhalogenation of tetra-O-acetyl-α-D-gulopyranosyl bromide (XLI).



XLI V

Compound V was isolated in good yield (60%), but since no experimental details were reported for the previous preparation (20), no comparison could be made with the zinc dust reduction.

The n.m.r. spectrum of V (Fig. 25, Table V) was

TABLE V

N.m.r. parameters for the tri-O-acetylated aldohexose glycals in deuteriochloroform (100 MHz).

Chemical shifts, τ value					
H_1	H_2	H_3	H_4	$H_{5,6,6'}$	Acetyl
Tri-O-acetyl-1,2-dideoxy-D-*arabino*-hex-1-enopyranose (I) (26)					
3.47	5.19	4.66	4.80	5.71-5.91	7.89 7.93 8.01
Tri-O-acetyl-1,2-dideoxy-D-*lyxo*-hex-1-enopyranose (IV) (26)					
3.54	5.27	4.44	4.57	5.6-6.0	7.87 7.91 7.96
Tri-O-acetyl-1,2-dideoxy-D-*xylo*-hex-1-enopyranose (V)					
3.37	4.85-5.15	4.85-5.15	4.85-5.15	5.7-5.8	7.88 7.93
Tri-O-acetyl-1,2-dideoxy-D-*ribo*-hex-1-enopyranose (VI)					
3.45	5.05	4.53	4.84	5.5-5.9	7.90 7.95

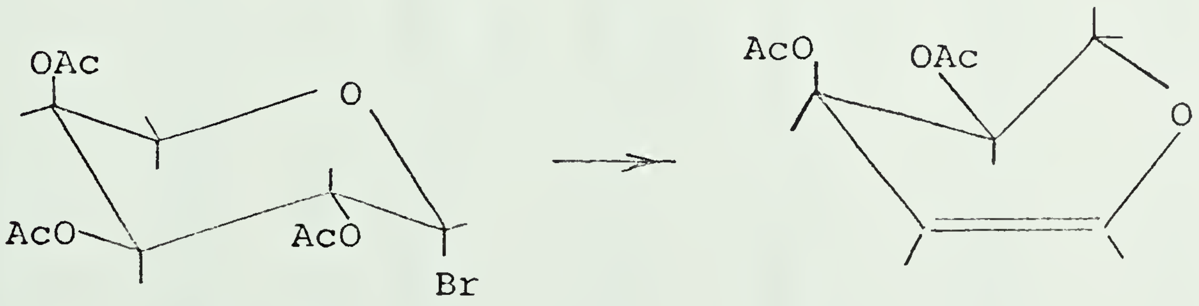
TABLE V (Cont'd)

Approximate coupling constants, Hz

	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
Tri-O-acetyl-1,2-dideoxy-D-*arabino*-hex-1-enopyranose (I) (26)					
	6.4	1.3	3.2	6.4	6.8
Tri-O-acetyl-1,2-dideoxy-D-*lyxo*-hex-1-enopyranose (IV) (26)					
	6.2	1.7	2.5	4.6	1.8
Tri-O-acetyl-1,2-dideoxy-D-*xylo*-hex-1-enopyranose (V)					
	6.1	-	-	-	-
Tri-O-acetyl-1,2-dideoxy-D-*ribo*-hex-1-enopyranose (VI)					
	6.0	-	6.0	4.0	10.0

comparable to the spectra of other hexopyranose glycals. As in the case of tri-O-acetyl-1,2-dideoxy-D-*ribo*-hex-1-enopyranose (VI), there was no discernible allylic coupling constant. Again, this was indicative of a rather small (35°) dihedral angle between the protons at C2 and C3. Thus, the 3-acetoxy group was held in a nearly axial orientation, as found for compound VI.

The magnesium amalgam reduction of tri-O-acetyl-β-L-arabinopyranosyl bromide (XXI) was undertaken for two purposes. It was, of course, an extension of the technique into the pentopyranose series and therefore a further indication of the general applicability of the reduction. Secondly, the reduction product, di-O-acetyl-1,2-dideoxy-L-*erythro*-pent-1-enopyranose (XXVIII), was a necessary intermediate in a reaction sequence under investigation in this laboratory. Thus, a sample of the glycosyl bromide (XXI) was subjected to the amalgam reduction in the usual fashion.



XXI

XXVIII

TABLE VI

N.m.r. parameters (100 MHz) for the di-O-acetylated aldopentose glycals in deuteriochloroform.

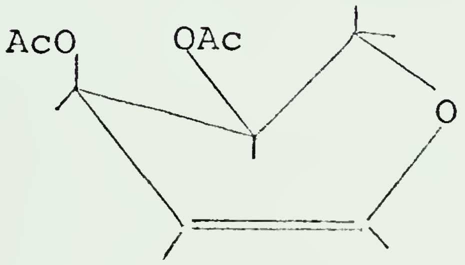
Chemical shifts, τ value

H_1	H_2	H_3	H_4	$H_{5,5'}$	Acetyl
Di-O-acetyl-1,2-dideoxy-L-*erythro*-pent-1-enopyranose (XXVIII)					
3.48	5.14	4.64	4.80	5.85-6.05	7.90
Di-O-acetyl-1,2-dideoxy-D-*threo*-pent-1-enopyranose (VIII) (26)					
3.69	5.18	4.95	5.10	5.9-6.4	7.91 7.93

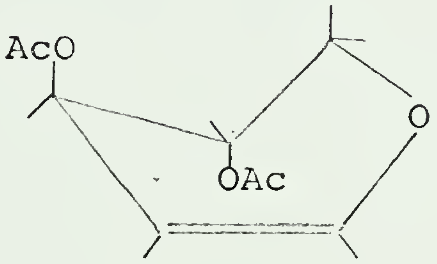
Approximate coupling constants, Hz

	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$	$J_{3,4}$
Di-O-acetyl-1,2-dideoxy-L-*erythro*-pent-1-enopyranose (XXVIII)				
	6.0	0.9	5.0	4.0
Di-O-acetyl-1,2-dideoxy-D-*threo*-pent-1-enopyranose (VIII) (26)				
	6.0	0.8	4.7	3.3

Compound XXVIII, unfortunately known only as a liquid, was obtained in 97.5% yield. The n.m.r. spectrum (Fig. 12, Table VI) of this material was completely in accordance with the conformation shown above. The value of the allylic coupling constant was similar to that reported by O'Neill (26) for di-O-acetyl-1,2-dideoxy-D-threo-pent-1-enopyranose (VIII).

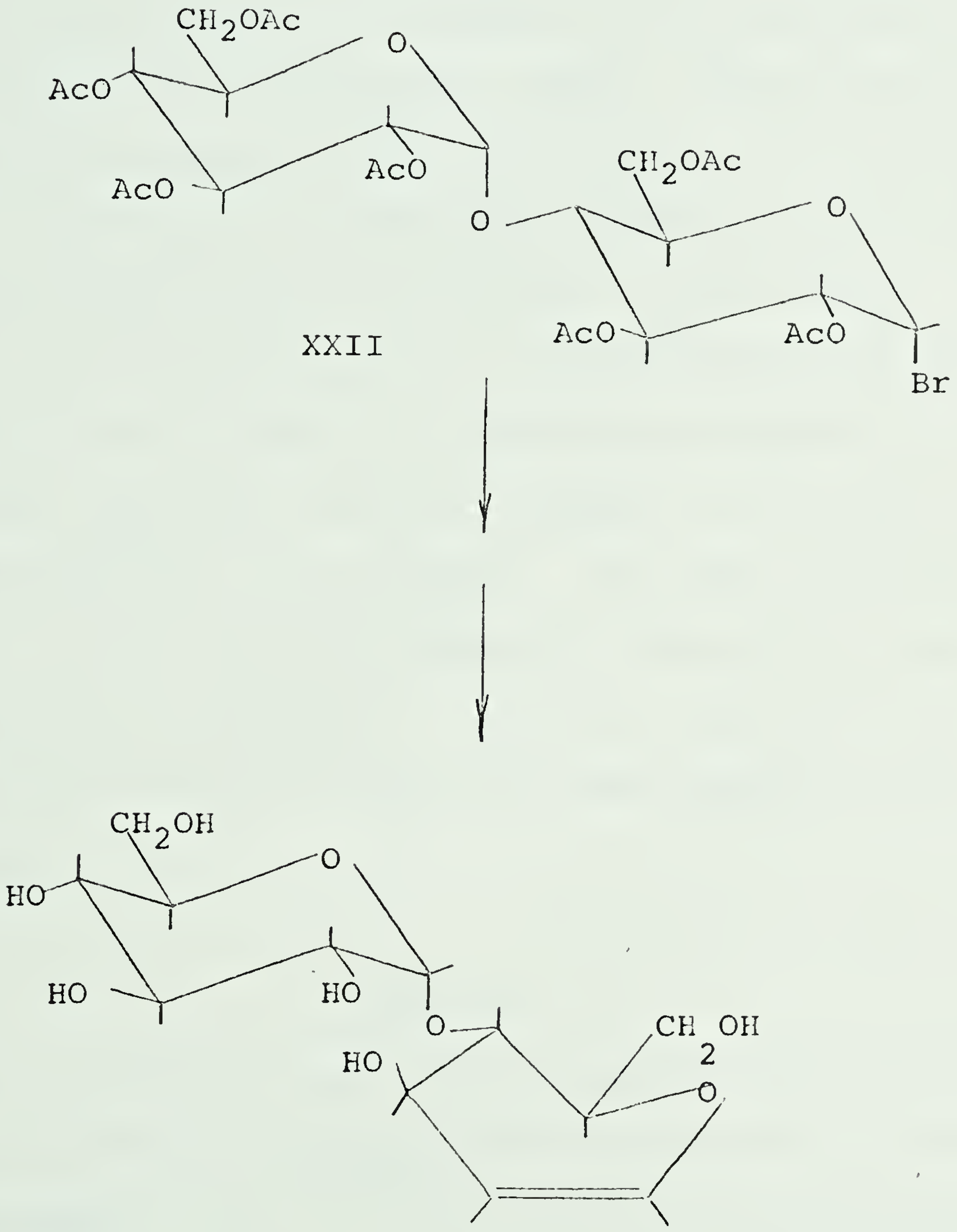


XXVIII



VIII

On the basis of the previously described theoretical relationship between the allylic coupling constant and the dihedral $\phi_{2,3}$, it was obvious that both compounds assumed a similar molecular shape in which the C-3 acetoxy group was somewhat less eclipsed with H-2 than was the C-3 hydrogen. This behavior was expected on consideration of the relative interactions of protons and acetoxy groupings. O'Neill's discovery of a comformation for VIII which had both acetoxy groups quasi-axial was suprising but, of course,


CH2OAc
AcO
AcO
AcO
O
O
CH2OAc
O
AcO
AcO
Br
CH2OH
HO
HO
HO
O
O
HO
CH OH
2
O

XXII

XXIX

in half-chair conformations, 1,3 diaxial interactions are negligible.

The possibility of the usage of the magnesium amalgam reduction in the disaccharide field was demonstrated by the preparation of 1,2-dideoxy-4-O-(α-D-glucopyranosyl)-D-*arabino*-hex-1-enopyranose (XXIX). Hepta-O-acetyl-α-D-maltosyl bromide (XXII) was treated with the amalgam in the same fashion as previously described and the unsaturated disaccharide was obtained in good yield. The acetylated compound did not crystallize and, since it showed marked tendencies toward de-acetylation on handling, it was saponified using the Zemplen (105) method before chromatography was attempted. Even when the deacetylated material was chromatographically homogeneous, however no crystals were obtained. The n.m.r. spectrum (Fig. 13, Table VII) left no doubt as to the identity of the compound.

TABLE VII

N.m.r. parameters (100 MHz) of 1,2-dideoxy-4-O-(α-D-glucopyranosyl)-D-*arabino*-hex-1-enopyranose in deuterium oxide.

H_1	H_2	H_3	$H_{1'}$	$H_{2'}$
Chemical shifts, τ value				
3.03	4.63	5.08	4.05	5.95

Approximate coupling constants, Hz		
$J_{1,2}$	$J_{1,3}$	$J_{2,3}$
6.0	1.4	3.0

Approximate coupling constants, Hz		
$J_{3,4}$	$J_{1',2'}$	$J_{2',3'}$
5.5	3.5	9.0

The anomeric proton of the unsaturated ring produced a readily identified signal which showed the expected couplings both with H-2 and H-3 as compared to the values listed in Table V for 1,2-unsaturated D-glucose. The couplings $J_{2,3}$ and $J_{3,4}$ were also closely comparable to the values shown by compound I. The patterns due to H-1 and H-2 of the saturated ring could be discerned and the values $J_{1,2}$ and $J_{2,3}$ were normal for a glucopyranosyl structure in

the Cl conformation.

Assurance that the magnesium amalgam reduction of hepta-O-acetyl-α-maltosyl bromide (XXII) led to the same product as the classical zinc dust in acetic acid method was given by an exact repetition of the reported method (40). A comparison was made of the i.r. spectra of the hexa-O-acetylmaltal (XV) with that of a re-acetylated sample of XXIX. The spectra were identical.

This concluded the investigation of magnesium amalgam as a reducing agent for the preparation of glycals. The material had been applied successfully to the deacetoxyhalogenation of seven different acetobromosugars and the yield was always good and often excellent. The amalgam technique appeared to be just as general as the classical method but the yields were much improved. An improvement in yield was of particular importance since the acetylated glycals are often exceedingly difficult to purify when not obtained virtually pure. In view of the previously mentioned usage of 1,2-unsaturated carbohydrate compounds as starting materials for the preparation of many biologically and commercially important products, the magnesium amalgam reduction can be expected to find wide application.

A second method of synthesis of acetylated 1,2-unsaturated aldoses resulted from an investigation of the reactions of tri-O-acetyl-1,2-O-(1-exo-2'-hydroxyethoxyethylidene)-α-D-glucopyranose (XXX).

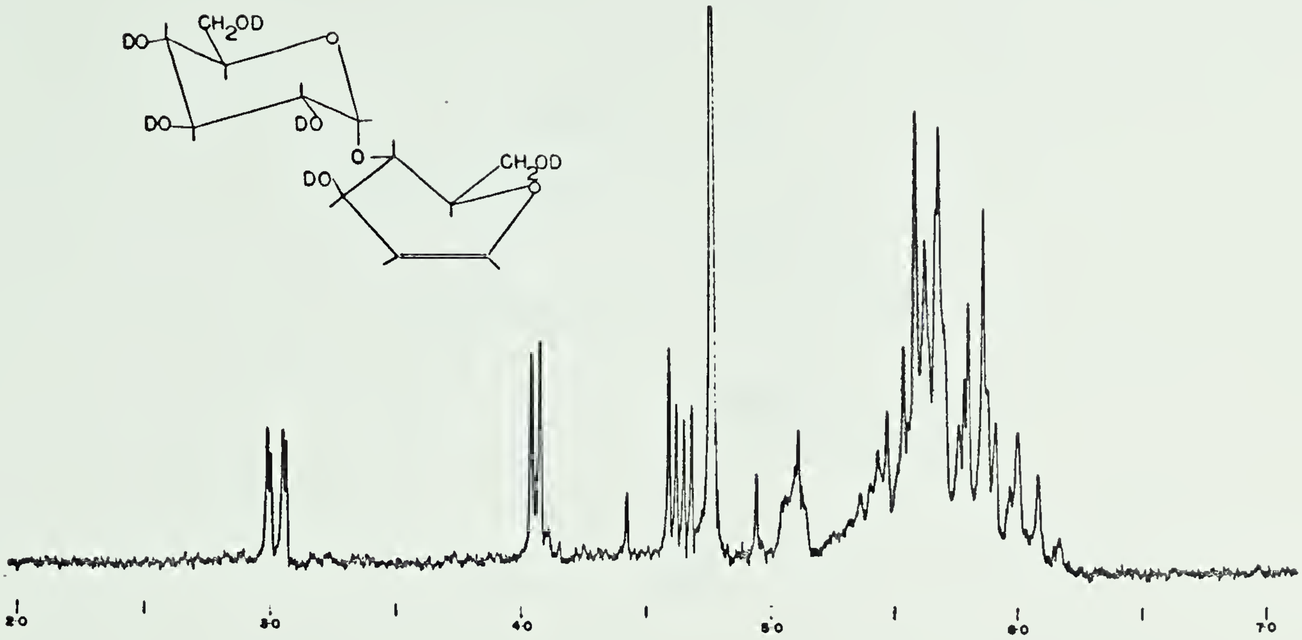


FIG. 13. N.m.r. spectrum (100 MHz) of 1,2-dideoxy-4-O-(α-D-glucopyranosyl)-D-arabino-hex-1-enopyranose (XXIX) (deuterium oxide)

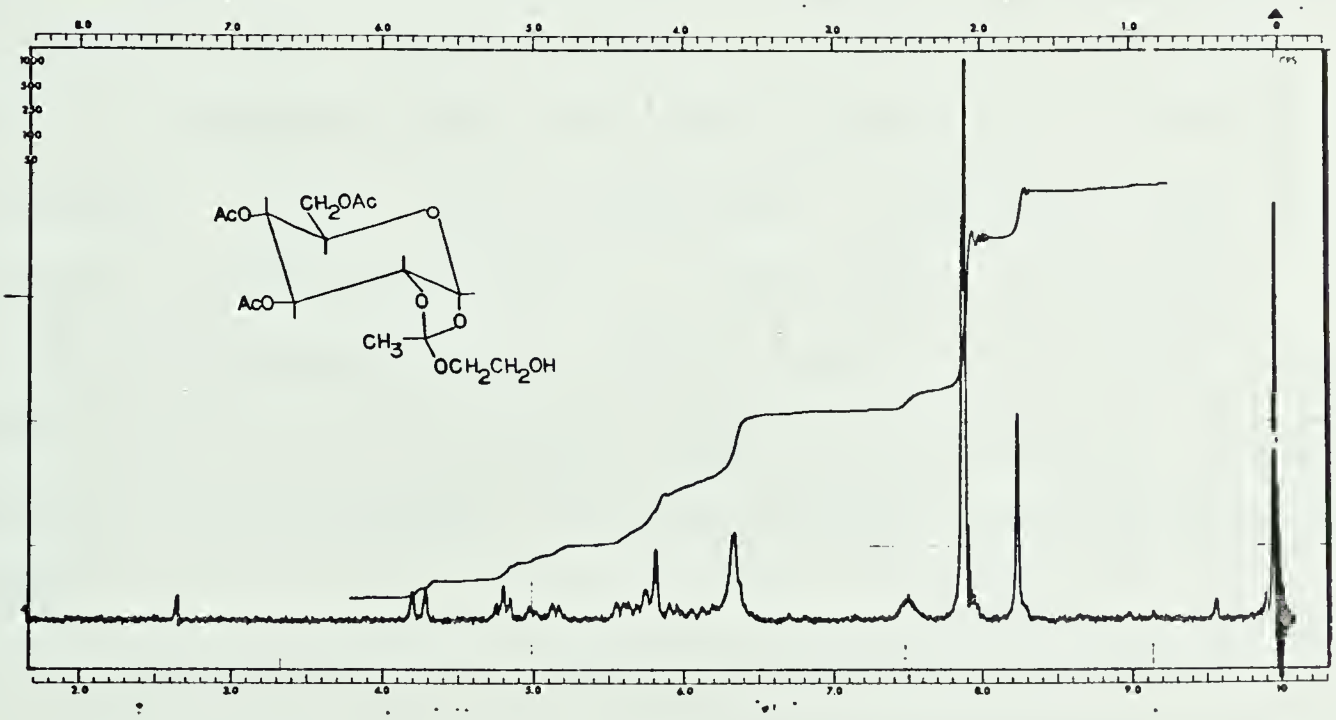
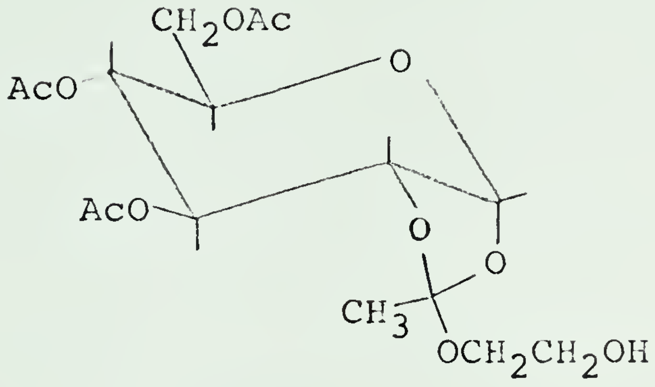


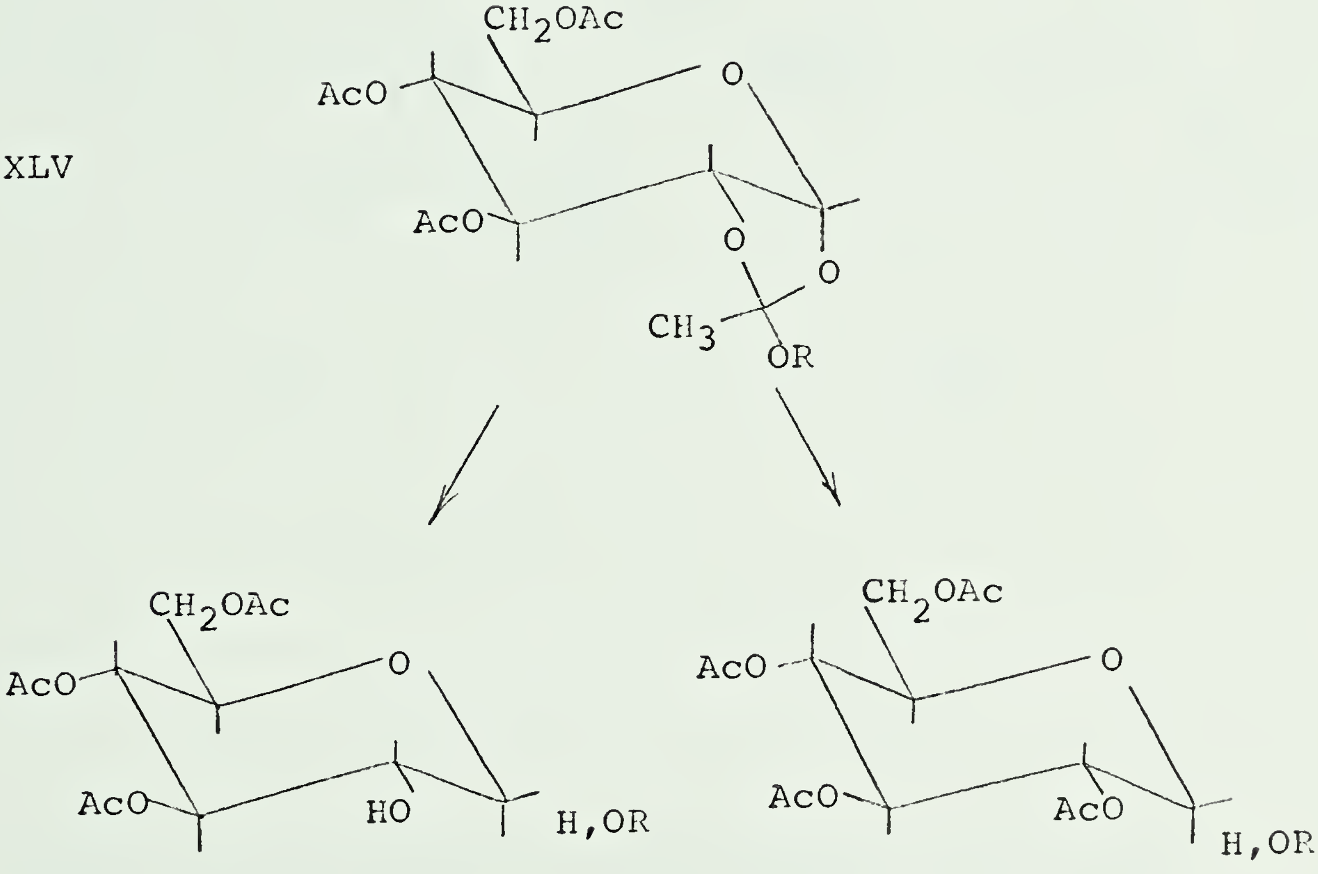
FIG. 14. N.m.r. spectrum (60 MHz) of tri-O-acetyl-1,2-O-(1-exo-2'-hydroxyethoxyethylidene)-α-D-glucopyranose (XXX) (deuteriochloroform)

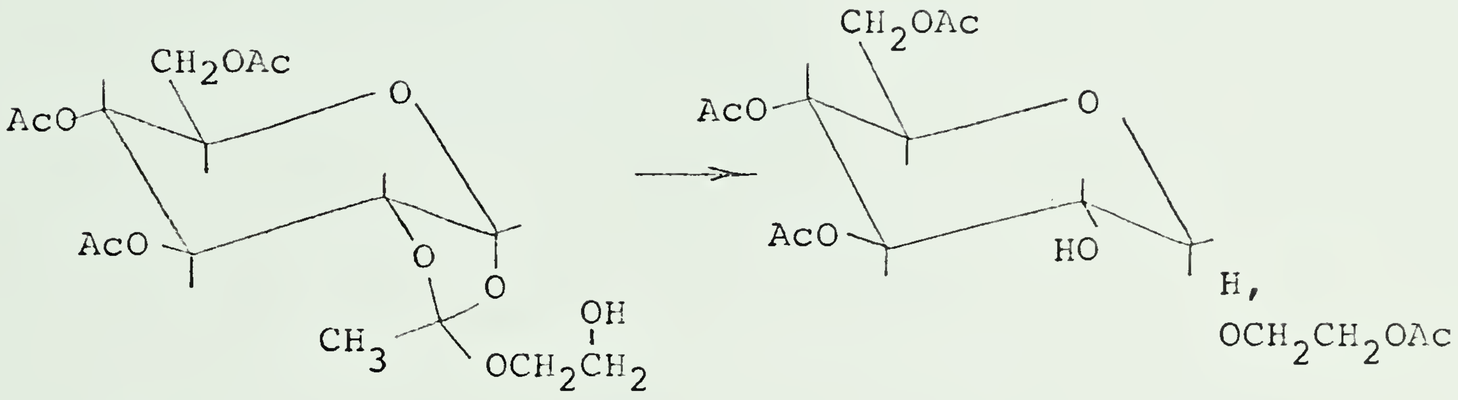


XXX

Morgan (58) and Detert (64) have examined the reactions of monohydric alcohols with tri-O-acetyl-α-D-glucopyranose 1,2-(alkyl orthoacetates) (XLV) in the presence of strong acids in anhydrous media and have reviewed the pertinent literature. Under these conditions , a dominant route of reaction is the formation of α- and β-alkyl 3,4,6-tri-O-acetyl-D-glucopyranosides. Thus it was of interest to examine whether the ethylene glycol orthoacetate XXX would provide 2'-acetoxyethyl 3,4,6-tri-O-acetyl-D-glucopyranosides (XLVI)

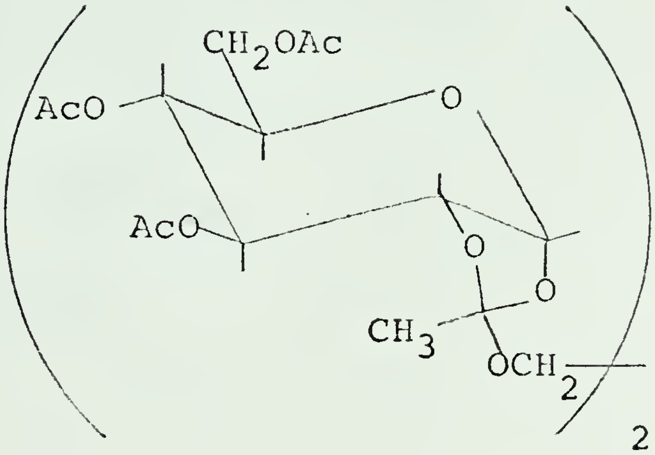
XLV


CH2OAc
AcO
O
AcO
O
O
CH3
OR
CH2OAc
AcO
O
AcO
HO
H,OR
CH2OAc
AcO
O
AcO
AcO
H,OR

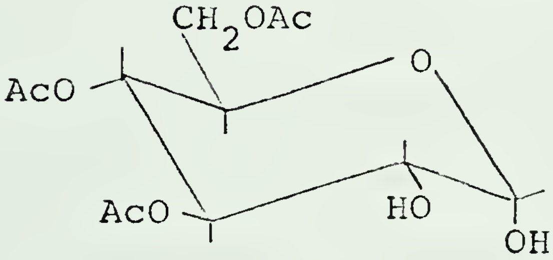

CH2OAc
AcO
O
AcO
O
O
OH
CH3
OCH2CH2
CH2OAc
AcO
O
AcO
HO
H,
OCH2CH2OAc

XXX XLVI

When the rearrangement was attempted in an inert solvent (methylene chloride or diethyl ether) using *p*-toluenesulfonic acid as catalyst, no such glycosides were formed. Instead, the reaction mixture contained two new carbohydrate structures; one of which was eventually assigned a bis-orthoacetyl structure (XXXI) and the other was found to be 3,4,6-tri-O-acetyl-α-D-glucopyranose (XXXII).

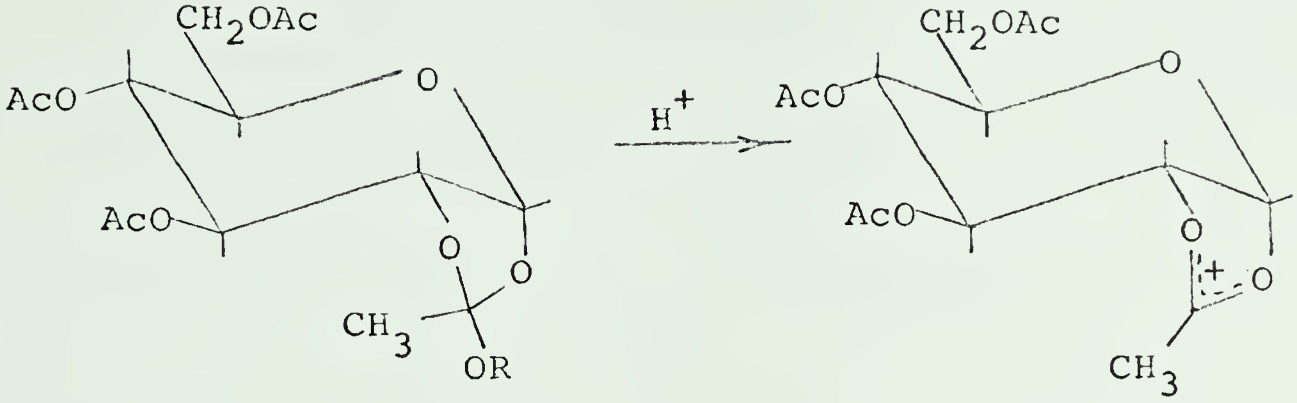

CH2OAc
AcO
O
AcO
O
O
CH3
OCH2
2

XXXI


CH2OAc
AcO
O
AcO
HO
OH

XXXII

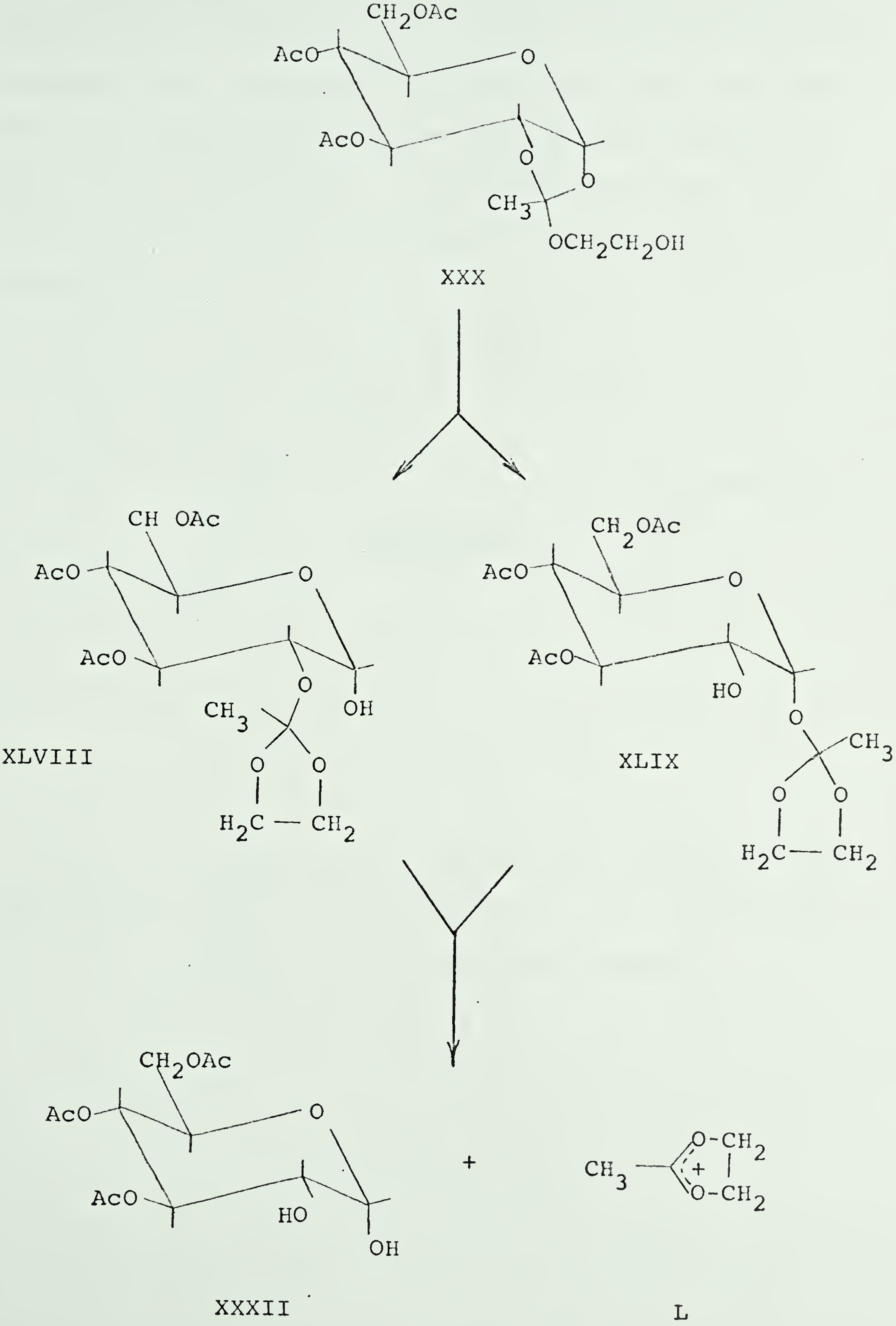
This was a rather surprising result and one which required a multiple reaction pathway to explain the material balance. Normally, orthoesters of this type had been known (58, 64) to proceed to an acetoxonium ion (XLVII) in a first step on protonation.



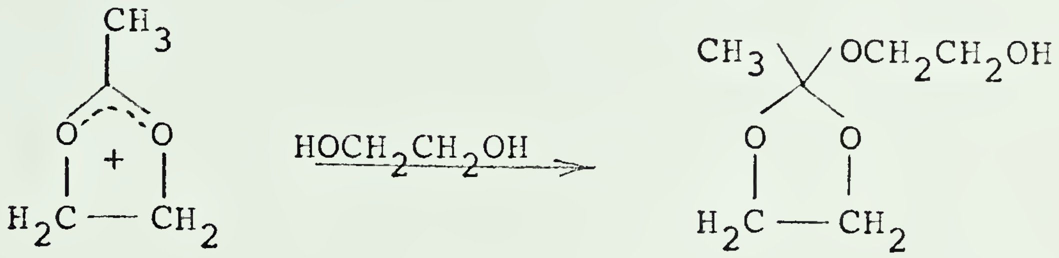
XXX

XLVII

Such ions are quite stable and, in fact, compounds containing them have been isolated (103). In the case of the glycol compound XXX, however, it appeared that another route was available. Since a product was the 1,2-diol (XXXII), the new reaction route probably involved rearrangement of the orthoacetate XXX to one or both of the isomeric orthoacetates XLVIII and XLIX. It would not be surprising that such an intramolecular rearrangement is facile since the free hydroxyl can participate in the opening of the dioxolane ring of XXX. Thus, the formation of the diol XXXII could be explained by the protonation of XLVIII and XLIX with the formation of a new acetoxonium ion L. This ion has been characterized as a stable salt (104).

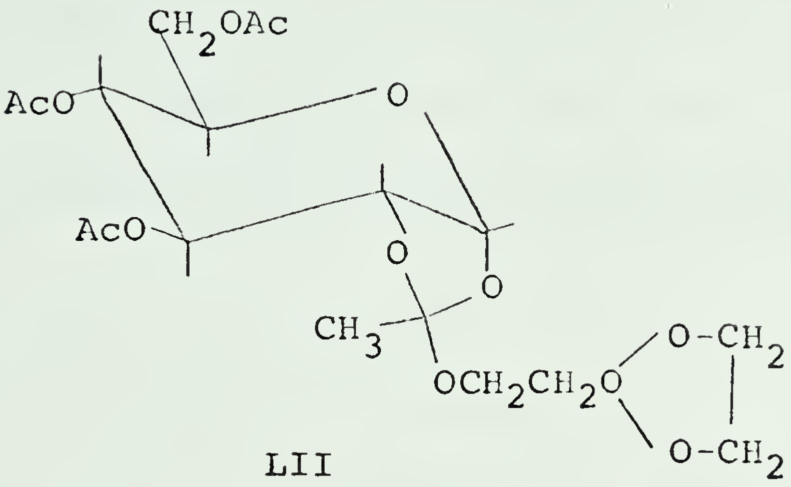

XXX
XLVIII
XLIX
XXXII
L

Concomitant with these transformations, ethylene glycol may be liberated by the simple transesterification mechanism well displayed by both Morgan (58) and Detert (64) which presumably involves the 1,2-acetoxonium ion XLVII as an intermediate. Thus, the acetoxonium ion L can be involved in the formation of ethylene glycol orthoacetate LI.

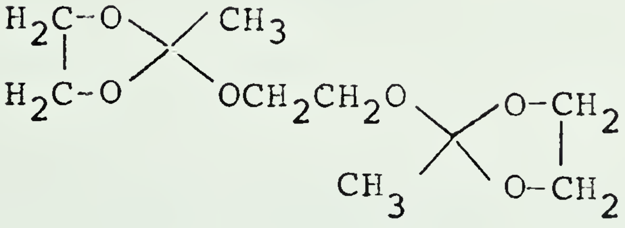


L LI

Of course, following these kinds of facile reaction routes, *bis*-ethylene glycol orthoesters of the type LII and LIII must also be present in the equilibrium mixture.



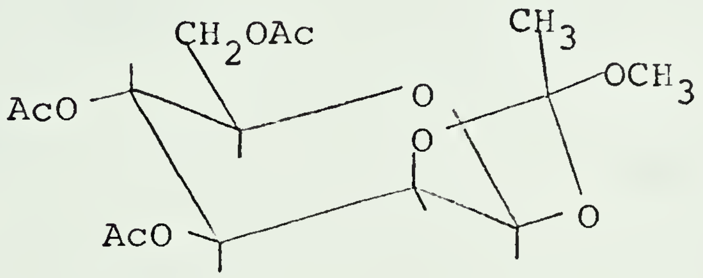
LII



LIII

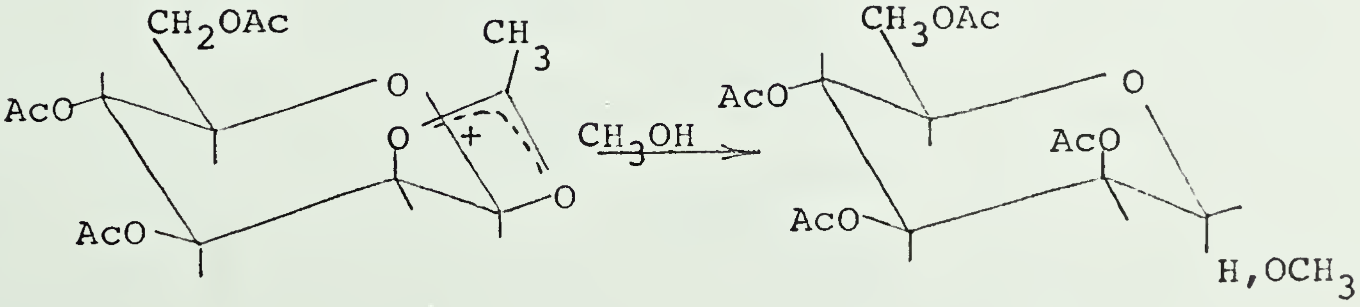
The point of main interest was that no glucopyranosides of ethylene glycol were observed. Both the anomeric configurations of 2'-hydroxyethyl D-glucopyranosides were synthesized (90, 91) and available for comparison purposes. It appeared then, that with the addition of an excess of ethylene glycol, this type of equilibration might be used

to prepare the 1,2-diol product XXXII in high yield. Such a reaction had been reported previously by Perlin (65) in a methanolysis of tri-O-acetyl-1,2-O-(1'-methoxyethylidene)-β-D-mannopyranose (XVII) but was accompanied by the formation of the methyl mannopyranosides (LIV) in 20% yield.



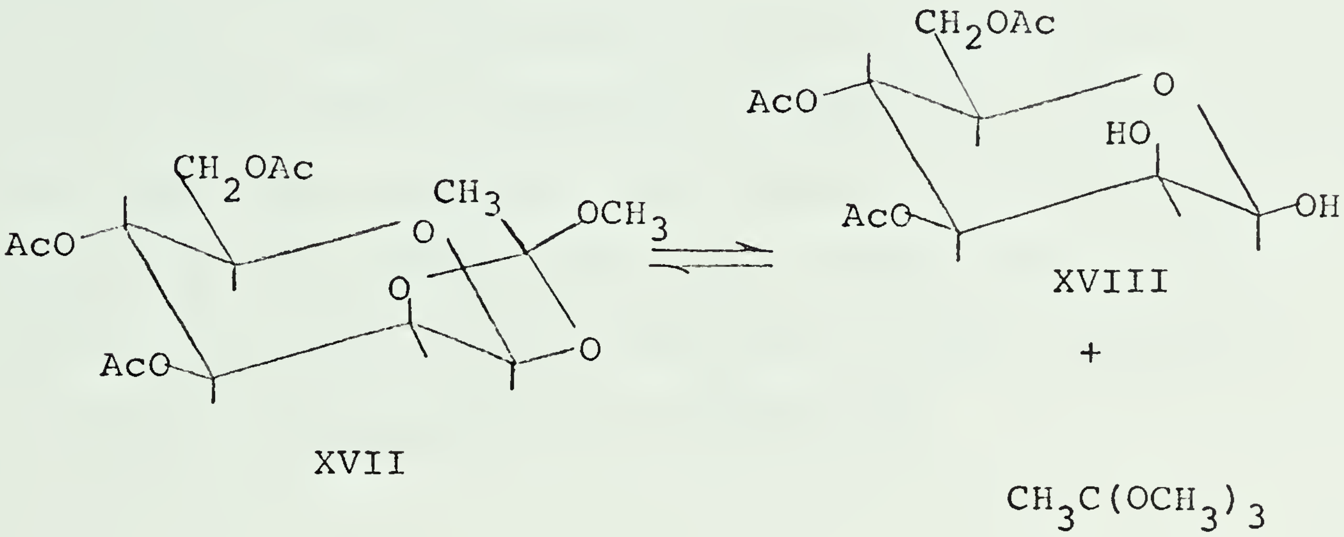
XVII

These (LIV) were produced through the attack by methanol on an acetoxonium ion.


CH₂OAc
AcO
AcO
CH3
+
CH3OH
CH3OAc
AcO
AcO
AcO
H,OCH3

LIV

In order for the diol (XVIII) to form under these conditions, the equilibrium must favour the formation of trimethyl orthoacetate (LV). Perlin (65) used a solution in methanol 0.1 M in XVII and 0.2 M in hydrogen chloride. This experiment was not repeated using tri-O-acetyl-1,2-O-(1-exo-methoxyethylidene)-α-D-glucopyranose (LVI). However, a similar reaction was conducted using 0.24 M

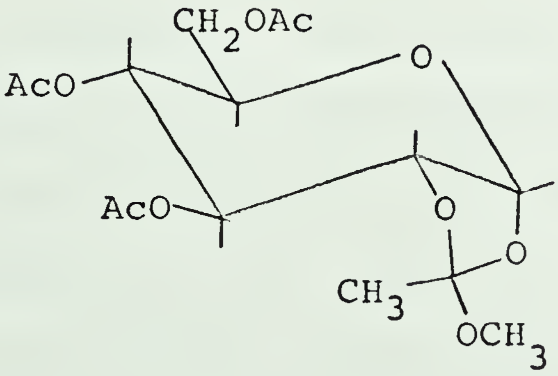

CH2OAc
AcO
AcO
CH3
OCH3
O
O
O
HO
OH
+

XVII

XVIII

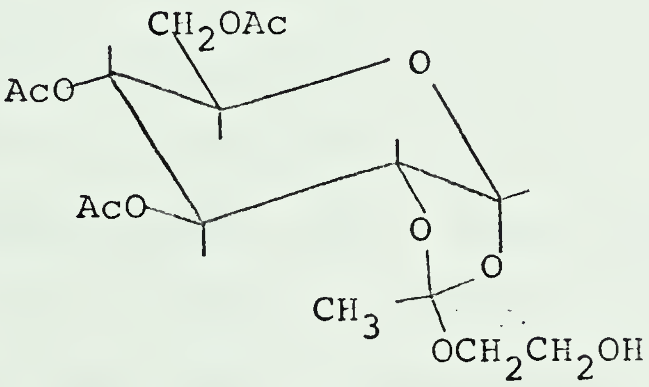
$CH_3C(OCH_3)_3$

LV


CH2OAc
AcO
AcO
O
O
O
CH3
OCH3

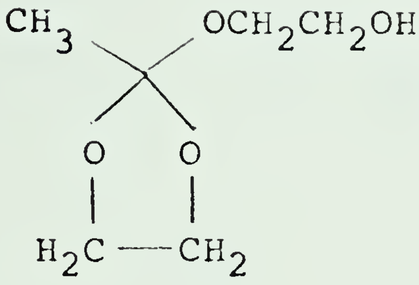
LVI

orthoacetate (LVI) and 0.06 M p-toluenesulfonic acid in 1:1 methanol-dimethylformamide at 25°. The reaction was followed by t.l.c. and found to give a product after 15 minutes which did not change in composition over the next 2.75 hours. N.m.r. analysis of this product showed it to contain about 40% of unreacted orthoacetate. On the other hand, when this experiment was repeated substituting ethylene glycol for the methanol (0.5 mole / mole) and starting with the ethylene glycol orthoacetate (XXX), there was no residual orthoacetate at equilibrium.

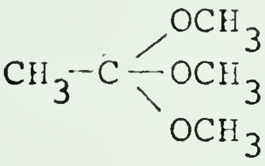


XXX

It was apparent, therefore, that the point of equilibrium was more favourable for the diol formation using ethylene glycol in the transesterification than when methanol was used. This situation was not surprising since an orthoester derived from ethylene glycol (LI) would be expected to be more favourable on an entropy basis than that from methanol.



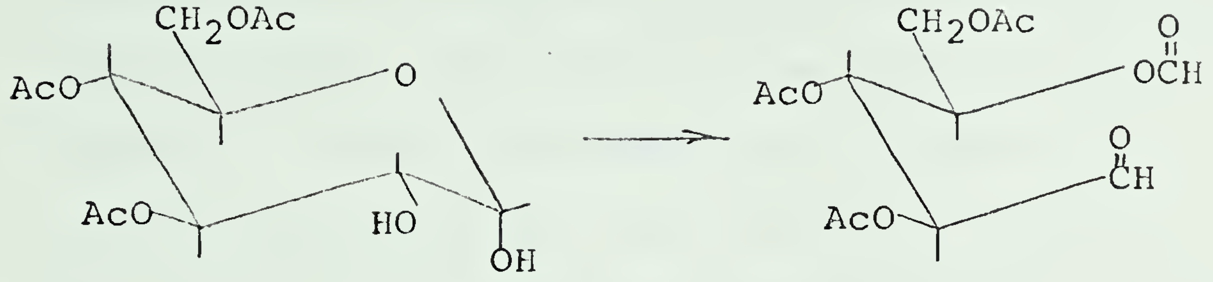
LI



$CH_3-C(OCH_3)_3$

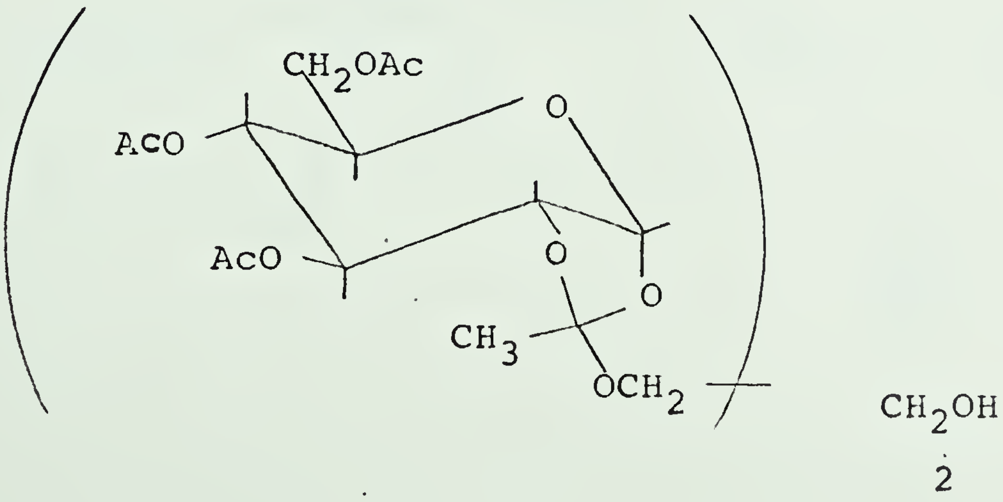
LV

The above observations prompted an investigation of the preparation of partially acetylated sugars with the 1 and 2-hydroxyl groups free. Such compounds would be of interest for a number of reasons including the preparation of the lower sugar by the way of an oxidation of the glycol grouping. Indeed, under appropriate conditions, the open chain derivative (LVII) of the sugar might be obtained. In this research, in view of our interest in the establishment of new approaches to the synthesis of glycals attention was directed to the utilization of such diols for this purpose.


CH2OAc
AcO
O
AcO
HO
OH
CH2OAc
O
OCH
AcO
O
CH
AcO

XXXII LVII

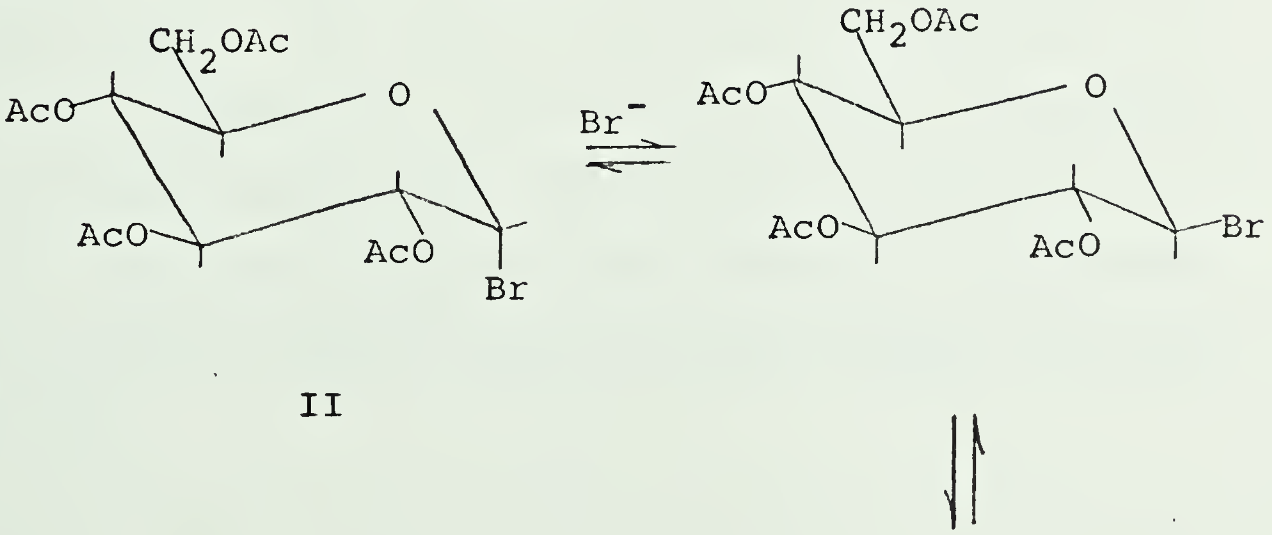
Two routes were available for the synthesis of tri-O-acetyl-1,2-O-(1-exo-2'-hydroxyethoxyethylidene)-D-glucopyranose (XXX) and the corresponding bis compound (XXXI). Both were utilized.


CH2OAc
AcO
O
AcO
O
O
CH3
OCH2
CH2OH
2

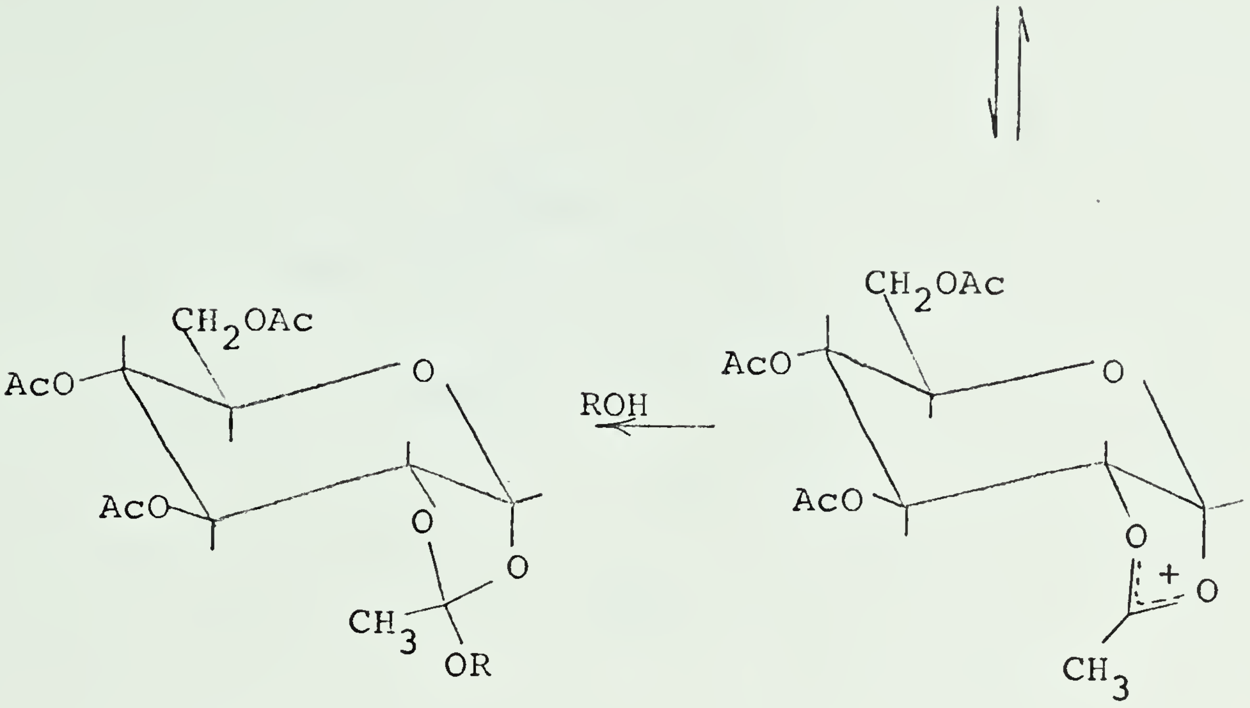
(XXX)

(XXXI)

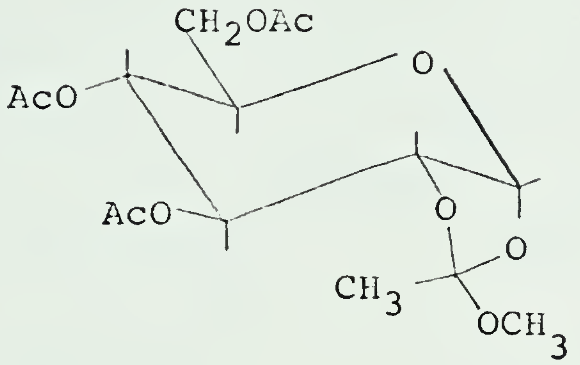
Initially, the materials were synthesized from tetra-O-acetyl-α-D-glucopyranosyl bromide (II) in the normal fashion. Two changes were made in the method described by Lemieux and Morgan (57). The earlier authors utilized *sym*-collidine both as a solvent and as a scavenger for the hydrogen bromide released in the synthesis. In our case, N,N-dimethylformamide was the solvent, and a calculated amount of 2,6-lutidine was added as the acid scavenger. The change of solvent made possible the use of sodium bromide rather than the less readily available tetra-n-butylammonium bromide as the source of bromide ion necessary to invert the anomeric configuration.



II



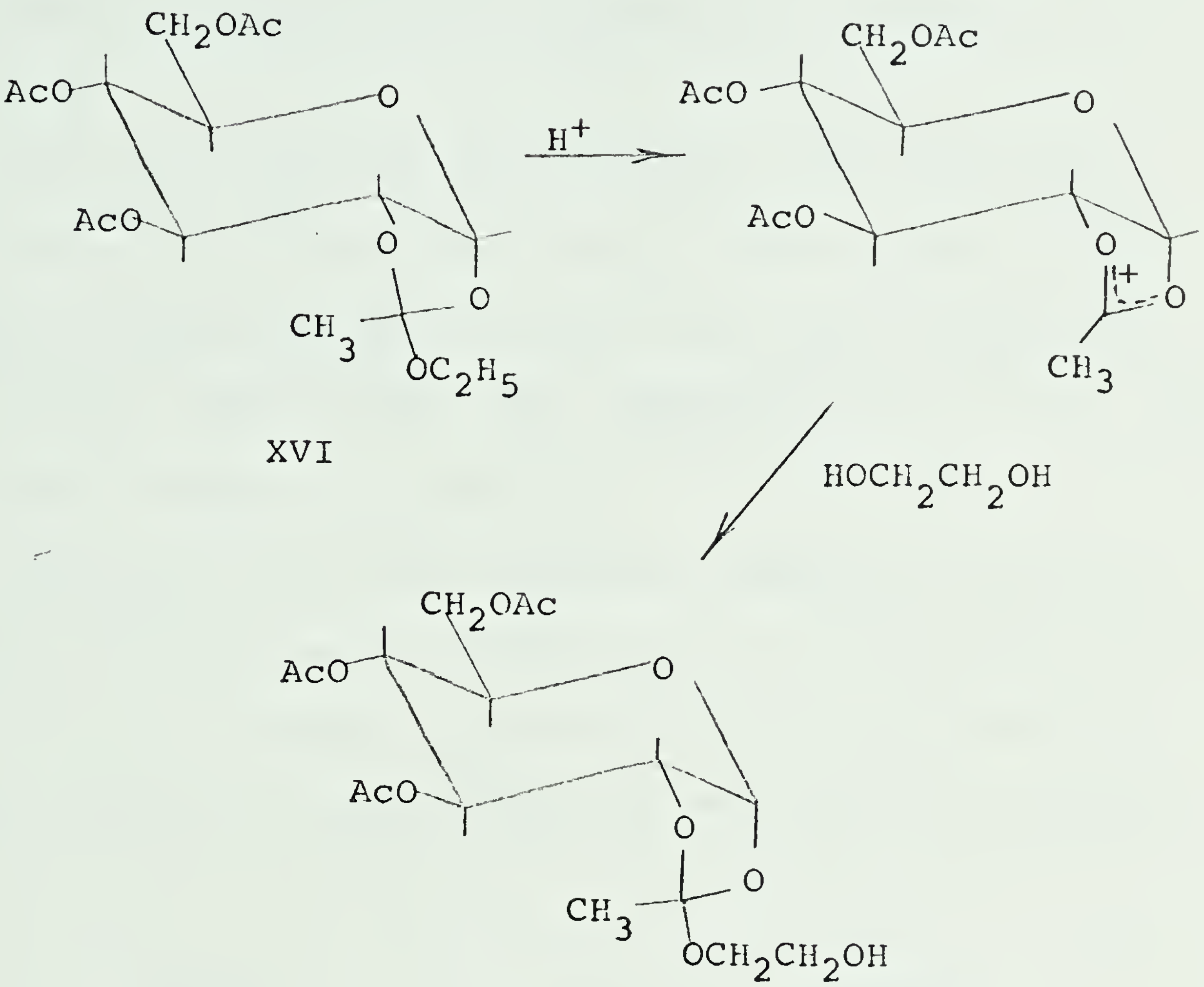
After a normal work-up, a t.l.c. indicated the presence of three compounds which were separated by silicic acid chromatography. A buffered solvent was necessary because of the sensitivity of the orthoacetates to acid. Thus, a small amount of 2,6-lutidine was added to the eluant. The smallest fraction was identified by its n.m.r. spectrum as tri-O-acetyl-1,2-O-(1-methoxyethylidene)-α-D-glucopyranose (LVI) which was isolated in 2% yield. This was assumed to have arisen in a transorthoesterification reaction which occurred during the chromatography.



LVI

Tri-O-acetyl-1,2-O-(1-exo-2'-hydroxyethoxyethylidene)-α-D-glucopyranose (XXX) was isolated in 26% yield as a syrup which spontaneously crystallized. The bis-orthoacetate (XXXI) also crystallized after isolation in 25% yield. Interestingly, the melting points of the monomer and dimer were essentially identical but a typical depression was shown on a mixed melting point determination.

Both of these compounds were also produced in an acid catalyzed transorthoesterification reaction of tri-O-acetyl-1,2-O-(1-exo-ethoxyethylidene)-α-D-glucopyranose (XVI).


CH2OAc
AcO
AcO
O
CH3
OC2H5
H+
CH2OAc
AcO
AcO
O
CH3
HOCH2CH2OH
CH2OAc
AcO
AcO
O
CH3
OCH2CH2OH

XVI

XXX

Experimentally, tri-O-acetyl-1,2-O-(1-*exo*-ethoxyethylidene)-α-D-glucopyranose was treated with 2 moles of ethylene glycol in the presence of about 1/2 mole of anhydrous *p*-toluenesulfonic acid. Again silicic acid chromatography was necessary for the separation of the products. Tri-

O-acetyl-1,2-O-(1-exo-2'-hydroxyethoxyethylidene)-α-D-glucopyranose (XXX) was obtained in 52% yield. The dimeric orthoacetate (XXXI), in this case, only represented a 5.9% yield and unreacted starting material was recovered in 28% yield.

The n.m.r. spectra of the monomer (XXX) and dimer (XXXI) were very similar and that of the monomer is shown in Fig. 14, and compared in Table VIII with the spectrum of the known compound XVI. The comparison is so close that no further comment is necessary.

The next step in the sequence leading to 3,4,6-tri-O-acetyl-D-glucopyranose (XXXII) was to be the transorthoesterification reaction in which the orthoacetyl function became completely removed from the carbohydrate structure.

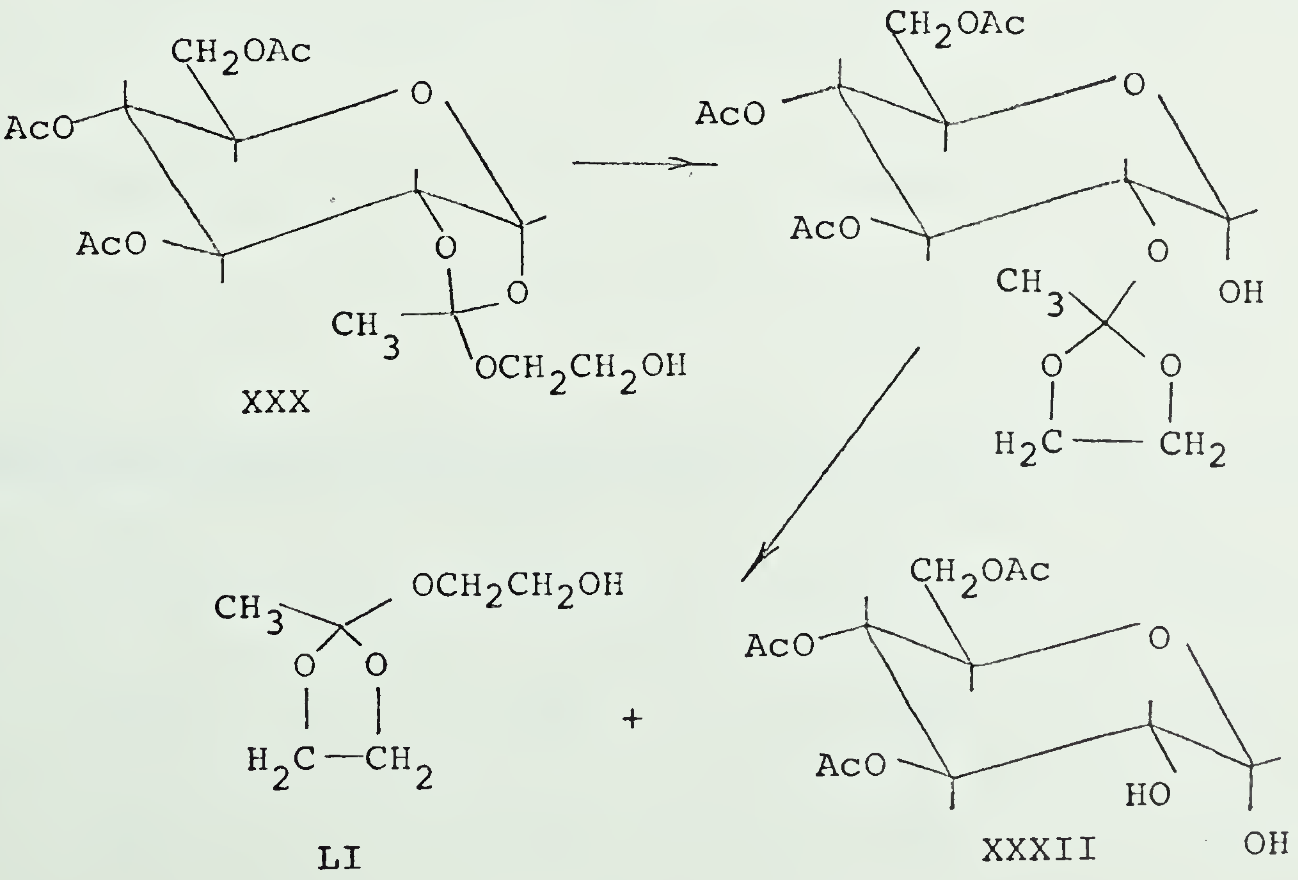

CH2OAc
AcO
AcO
O
O
O
CH3
OCH2CH2OH
XXX
CH2OAc
AcO
AcO
O
O
OH
CH3
O
O
H2C
CH2
CH3
OCH2CH2OH
O
O
H2C
CH2
LI
+
CH2OAc
AcO
AcO
O
HO
OH
XXXII

TABLE VIII

A comparison of the n.m.r. parameters (60 MHz) of tri-O-acetyl-1,2-O-(1-exo-2'-hydroxyethoxyethylidene)-α-D-glucopyranose (XXX) in deuteriochloroform with those of tri-O-acetyl-1,2-O-(1-exo-ethoxyethylidene)-α-D-glucopyranose (XVI)(57)

Chemical shifts, τ value

	H_1	H_3	H_4	$H_{5,6,6'}$
XXX	4.25	4.79	5.08	5.5-6.2
XVI	4.28	4.81	5.09	5.5-5.9

Chemical shifts, τ value

	Glycol	Hydroxyl	Acetyl	C-methyl
XXX	6.33	7.5	7.89	8.25
XVI	-	-	7.90	8.27

Approximate coupling constants, Hz

	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
XXX	5.5	2.8	2.8	9.0
XVI	5.0	2.8	2.8	9.0

In the experimental technique actually used, the carbohydrate orthoacetate compounds containing glycol were not, in fact, the starting materials. Rather, a several stage equilibration reaction was carried out which utilized more readily available materials. The first route was based on an extended transorthoesterification of tri-O-acetyl-1,2-O-(1-exo-ethoxyethylidene)-α-D-glucopyranose (XVI). Thus, when this compound was treated with an excess of ethylene glycol and an acid catalyst, the expected products were the exchanged orthoacetates, that is, compounds XXX and XXXI. On continued treatment, the processes leading to the removal of the orthoacetyl function from the carbohydrate structure would take place and one hoped to isolate compound XXXII. The reaction did indeed proceed and 3,4,6-tri-O-acetyl-α-D-glucopyranose (XXXII) was isolated in 77% yield. Some tetra-O-acetyl-D-glucopyranose was also formed in aqueous hydrolysis of orthoacetate structures. On the basis of the work of Detert (64), this was expected to be 2,3,4,6-tetra-O-acetyl-α-D-glucopyranose but no further study of the compound was undertaken here.

The n.m.r. spectrum of 3,4,6-tri-O-acetyl-α-D-glucopyranose (XXXII), recorded in Table IX, was entirely in accord with the Cl conformation shown. The small coupling $J_{1,2}$ established the α-anomeric configuration and the

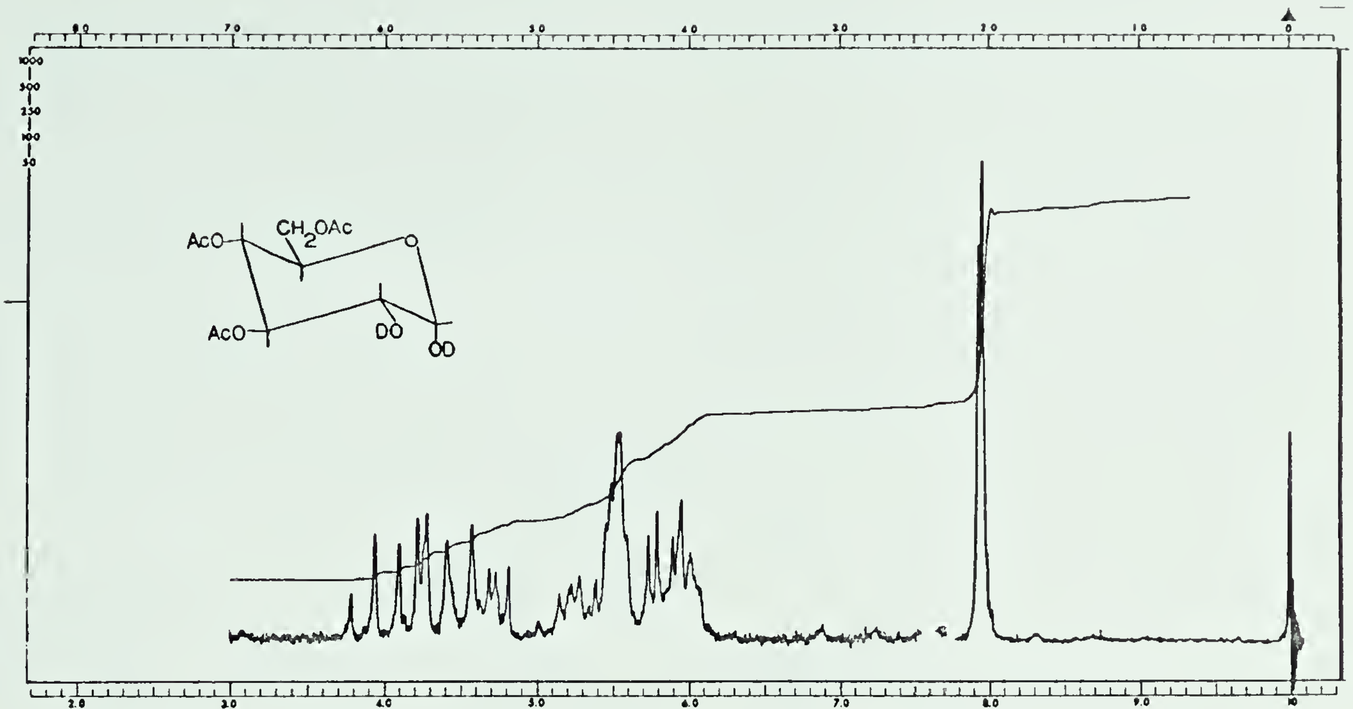


FIG. 15. N.m.r. spectrum (60 MHz) of 3,4,6-tri-O-acetyl-α-D-glucopyranose (XXXII) (deuteriopyridine)

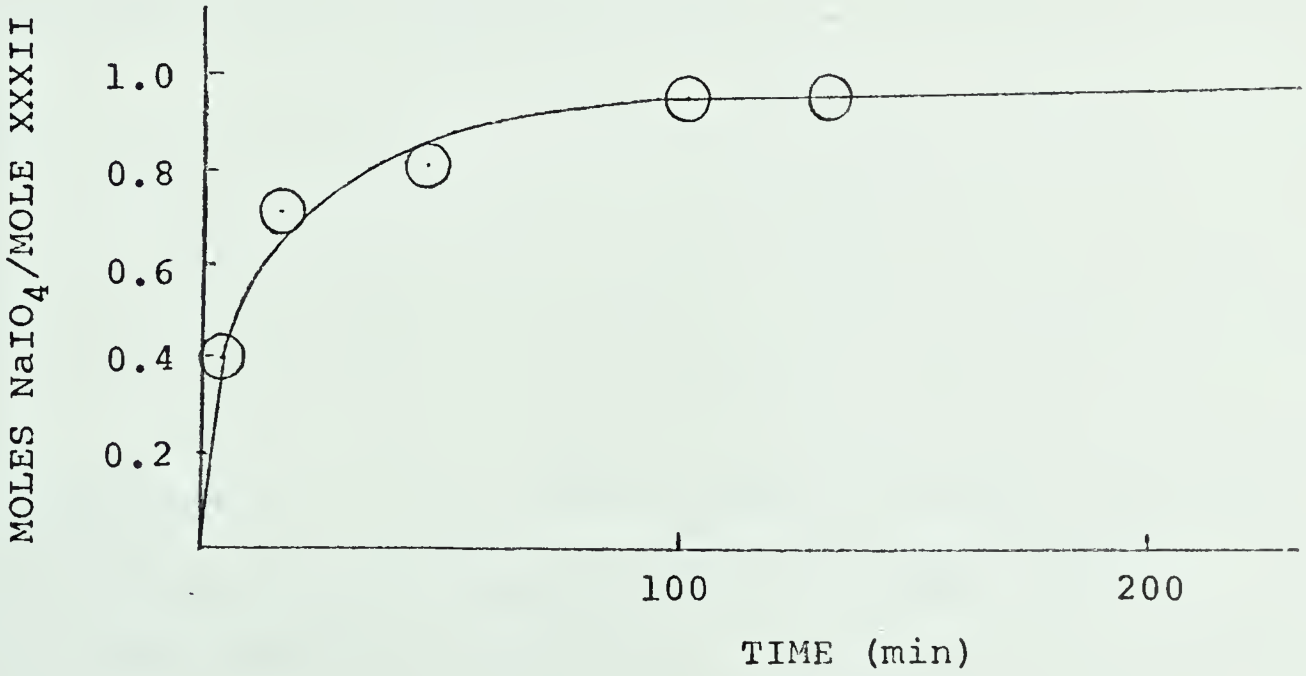
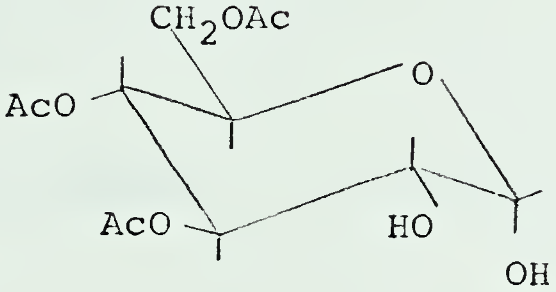


FIG. 16. Plot of sodium periodate oxidation of 3,4,6-tri-O-acetyl-α-D-glucopyranose (XXXII)


CH2OAc
O
AcO
AcO
HO
OH

XXXII

large couplings $J_{2,3}$, $J_{3,4}$ and $J_{4,5}$ made it plain that the protons at C-2, C-3, C-4 and C-5 were all trans and diaxial to their adjacent neighbors.

TABLE IX

N.m.r. parameters (60 MHz) of tri-O-acetyl-α-D-glucopyranose in deuteriopyridine.

Chemical shifts, τ value		
H_1	H_2	H_3
4.23	5.85	3.92

Chemical shifts, τ value		
H_4	$H_{5,6,6'}$	Acetyl
4.56	5.1-5.7	7.95

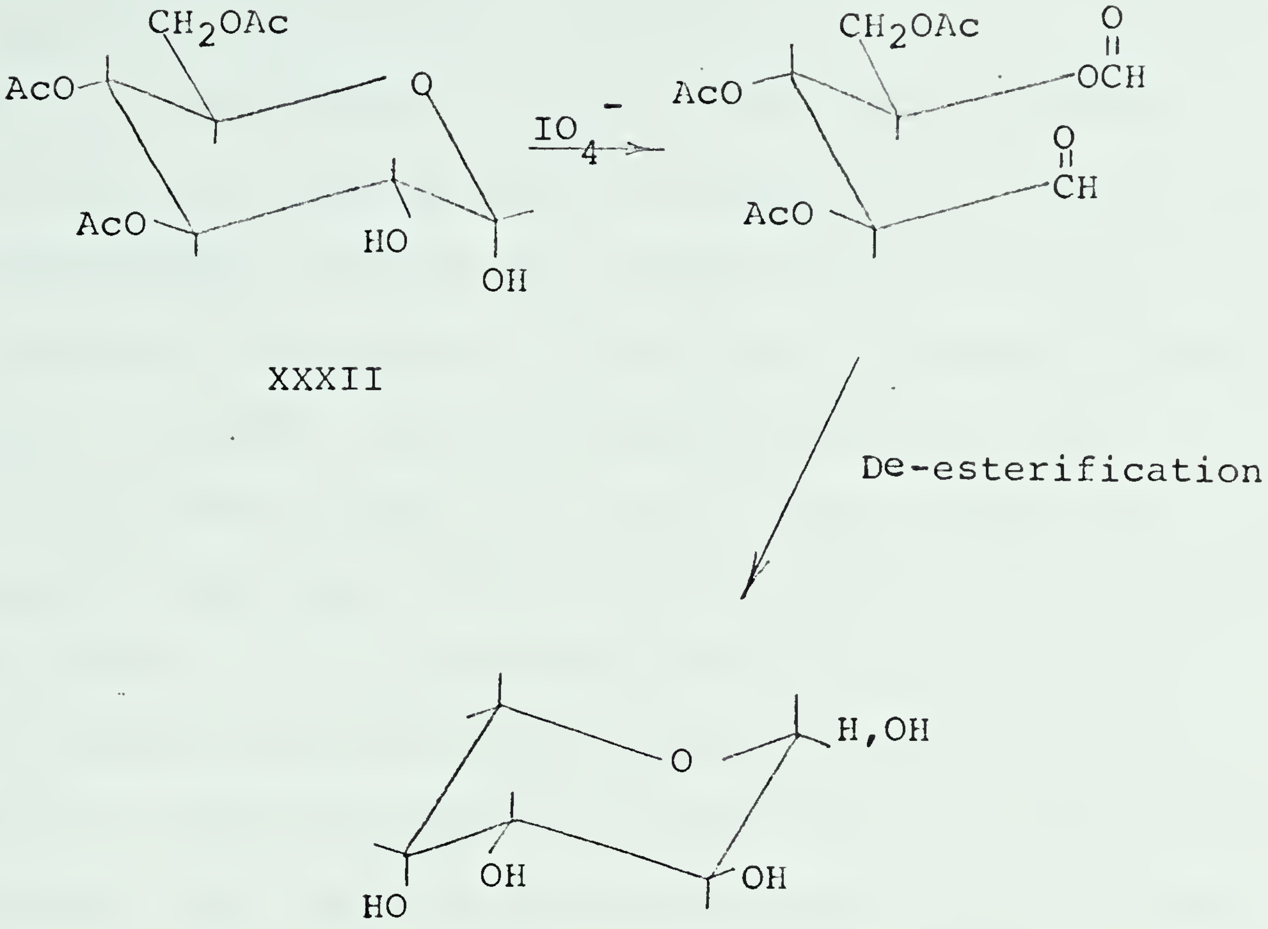
Approximate coupling constants, Hz			
$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
3.0	9.5	9.5	9.5

Unfortunately, this compound was not obtained in a crystalline state, although Brigl and Schinle (51), in their preparation, reported a m.p. of 110 - 112°. In order to insure that both preparations led to the same product, the earlier method was repeated exactly. No crystalline material was obtained but a comparison of i.r. spectra

and on a t.l.c. showed that the two methods led to an identical end-product.

Since it was established that the orthoacetate exchange reaction would lead to good yields of carbohydrate "diol" products, the preparation was attempted utilizing tetra-O-acetyl-α-D-glucopyranosyl bromide (II) as starting material. The glycol orthoacetates XXX and XXXI were prepared and, without isolation, these were subjected to the conditions of exchange. In the end, 3,4,6-tri-O-acetyl-α-D-glucopyranose (XXXII) was isolated in 60.5% over-all yield.

The reaction of the tri-acetate (XXXII) with excess sodium periodate was measured by the method of Mueller and Friedberger (95). It was apparent from the results (Fig. 16) that each mole of XXXII consumed one mole and only one mole of periodate. This was, of course, exactly the expected result. A larger scale oxidation from which the product was isolated and de-esterified allowed identification of the latter as D-arabinose.


CH2OAc
AcO
AcO
HO
OH
O
IO4-
CH2OAc
AcO
AcO
OCH
CH
De-esterification
H,OH
O
OH
OH
HO

XXXII

D-arabinose

The next compound in the synthetic series was to be the tri-O-acetyl-1,2-O-p-toluenesulfonyl-D-glucose (XXXIV). That this compound could not be made by the use of p-toluenesulfonyl chloride in the usual fashion was demonstrated by the preparation of tri-O-acetyl-2-O-p-toluenesulfonyl-α-D-glucopyranosyl chloride (XXXIII). Thus, compound XXXII was treated with somewhat more than two moles of p-toluenesulfonyl chloride in the presence of pyridine as an acid

scavenger. The syrup obtained in 80% yield was readily identified as the glucosyl chloride by its n.m.r. spectrum (Fig. 17) as described in Table X. The most significant feature of this spectrum was the integration of the signal for the C-methyl group of the toluene function at τ 7.57. This indicated the presence of only one p-toluenesulfonyl group per molecule. Another interesting feature was the high-field acetyl signal at τ 8.25. Such a signal had previously been shown (106) to be attributable to an acetyl group adjacent to a p-toluenesulfonyl function. Thus, if the acetyl groups had not undergone a migration, and certainly a migration was not expected to occur under such conditions, then the lone p-toluenesulfonyl group in the molecule was necessarily located at C-2. The anomeric signal, however, had been subject to a 24 Hz downfield shift with respect that of the starting material, and therefore the anomeric centre bore a deshielding substituent. That this was chlorine was demonstrated by the positive halide test given by an acidified solution of XXXIII in aqueous methanol.

The formation of XXXIII was not surprising since such compounds had been reported previously in attempted preparations of anomeric p-toluenesulfonates. As mentioned in the introduction, the mechanism for their synthesis involves the reaction of the first formed anomeric

TABLE X

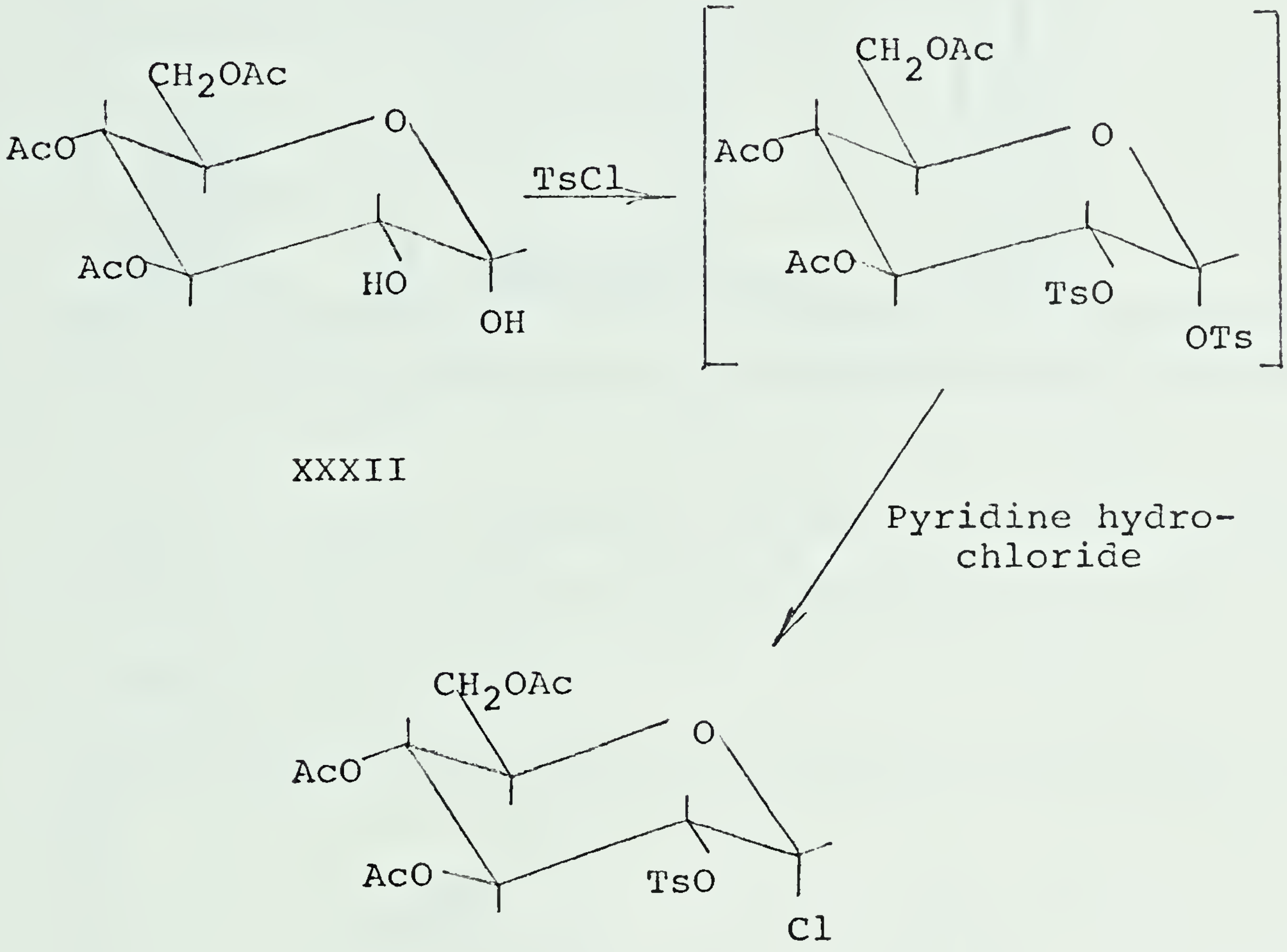
N.m.r. parameters (60 MHz) of tri-O-acetyl-2-O-p-toluenesulfonyl-α-D-glucopyranosyl chloride (XXXIII) in deuteriochloroform.

Chemical shifts, τ value			
H_1	H_2	H_3	H_4
3.83	5.33	4.50	4.92

Chemical shifts, τ value			
$H_{5,6,6'}$	Aromatic	C-methyl	Acetyl
5.5-6.0	2.1-2.8	7.57	7.91 8.00 8.25

Approximate coupling constants, Hz			
$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
4.0	9.5	9.5	9.5

p-toluenesulfonate with pyridine hydrochloride, a by-product in the normal reaction scheme.


CH2OAc
AcO
AcO
O
HO
OH
TsCl
CH2OAc
AcO
O
AcO
TsO
OTs
Pyridine hydrochloride
CH2OAc
AcO
O
AcO
TsO
Cl

XXXII

XXXIII

These anomeric p-toluenesulfonates are so reactive, in fact, that the only reported successful preparation required the use of the silver salt of p-toluenesulfonic acid in diethyl ether solution with the acetylated glycosyl bromide.

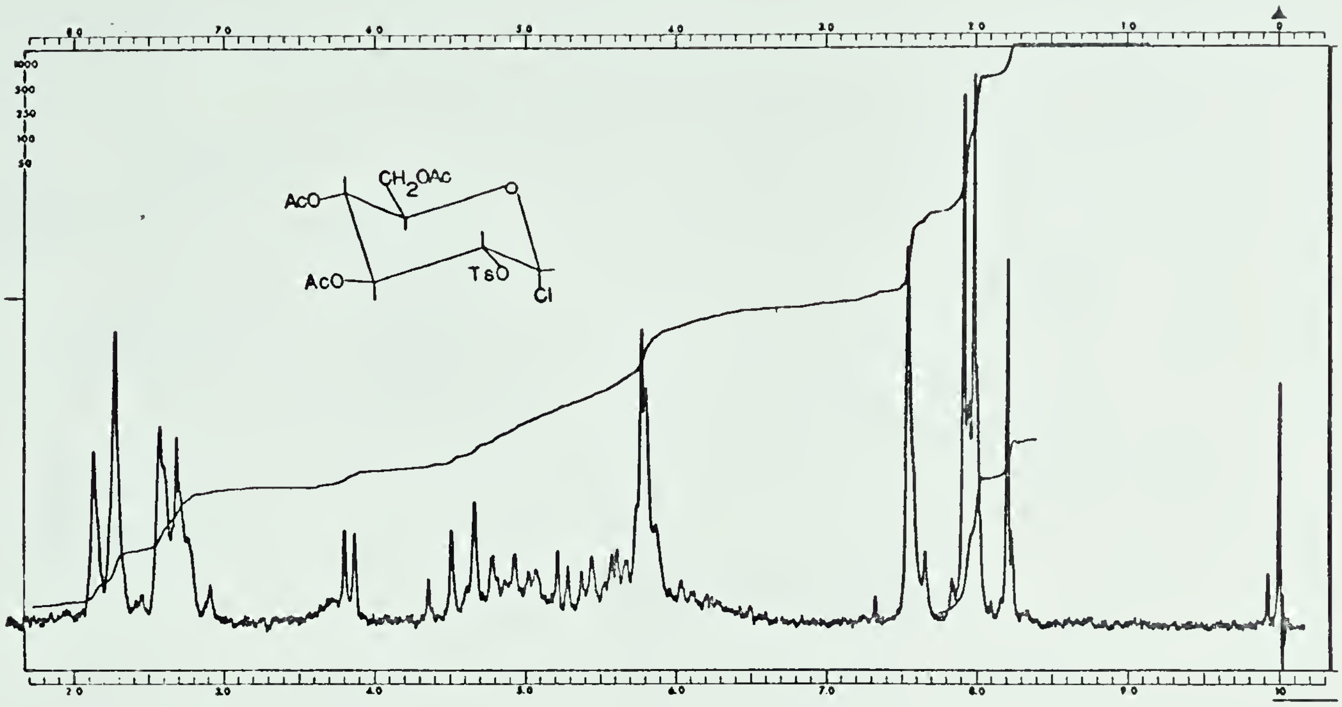


FIG. 17. N.m.r. spectrum (60 MHz) of 3,4,6-tri-O-acetyl-2-O-p-toluenesulfonyl-α-D-glucopyranosyl chloride (XXXIII) (deuteriochloroform)

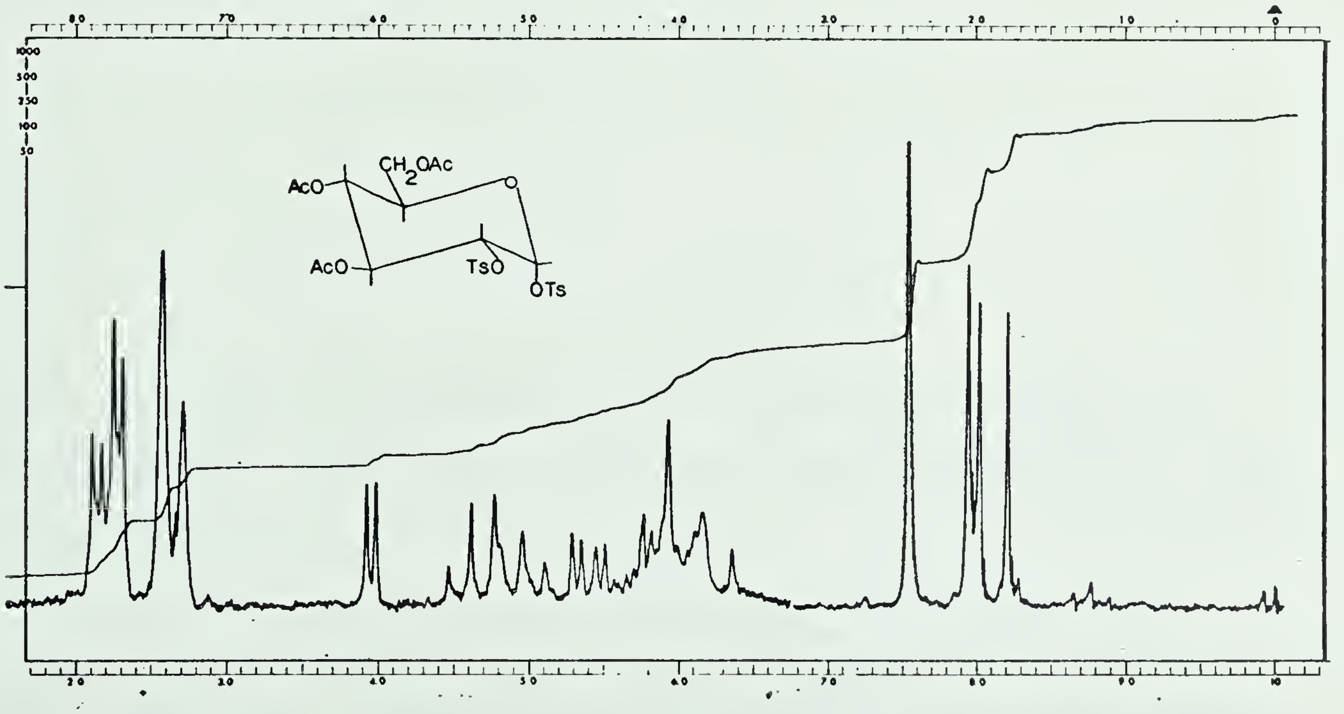
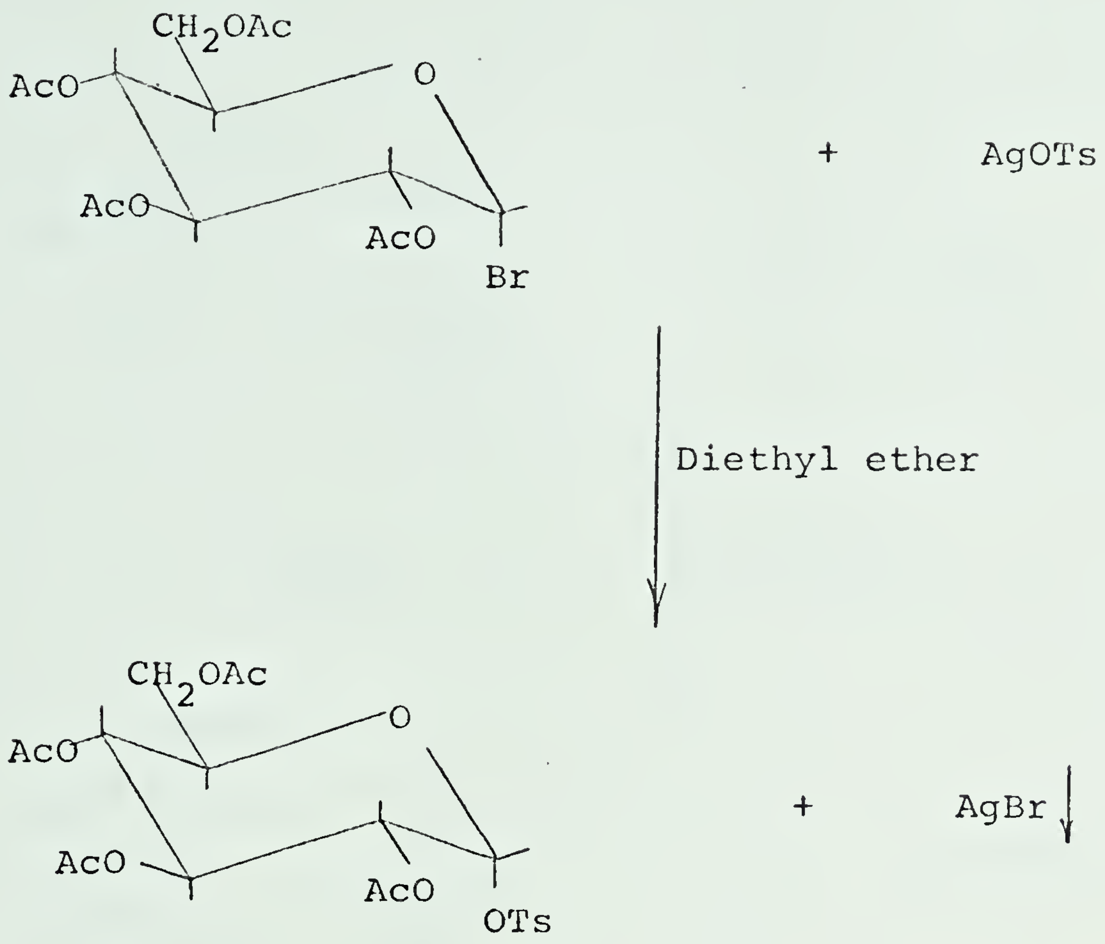


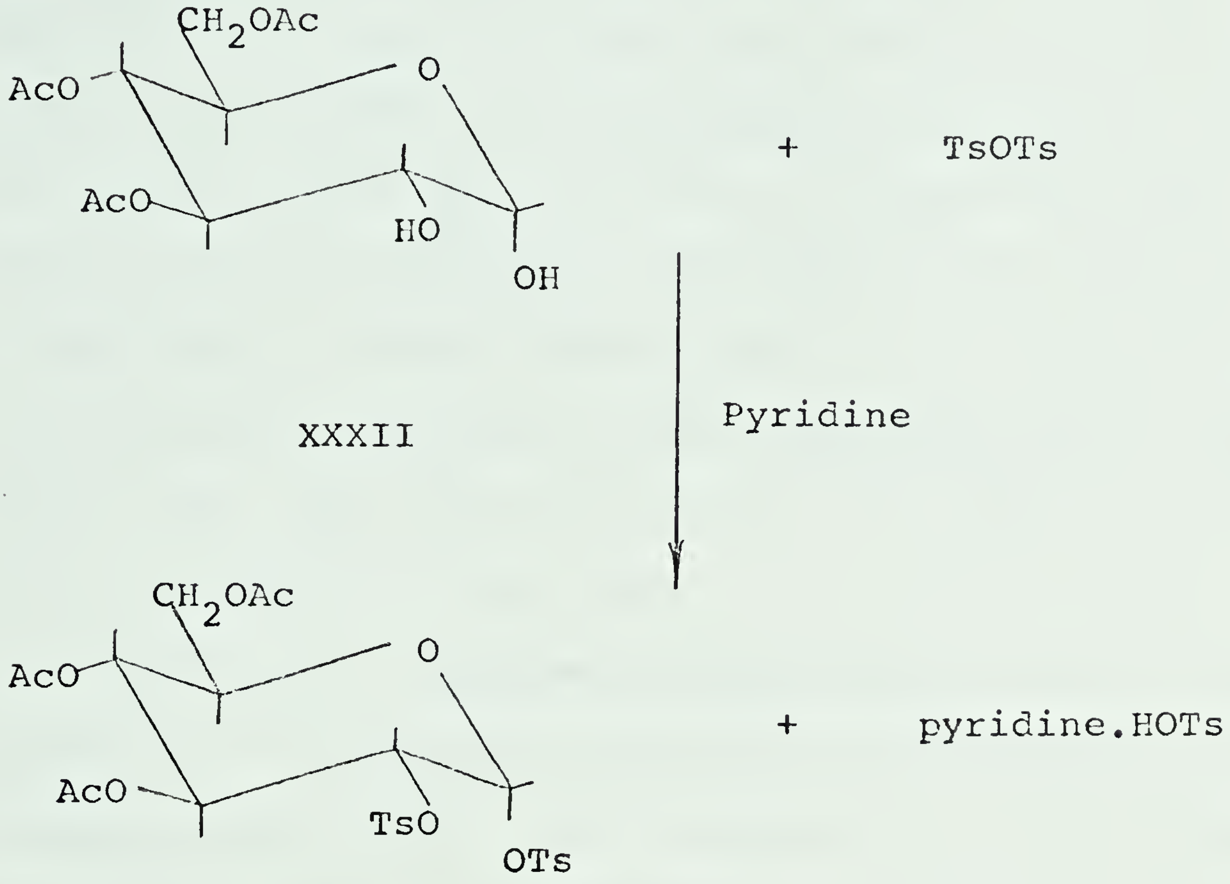
FIG. 18. N.m.r. spectrum (60 MHz) of tri-O-acetyl-1,2-di-O-p-toluenesulfonyl-α-D-glucopyranose (XXXIV) (deuteriochloroform)


CH2OAc
AcO
O
AcO
AcO
Br
+
AgOTs
Diethyl ether
CH2OAc
AcO
O
AcO
AcO
OTs
+
AgBr

Thus, Helferich and Gootz (107) isolated a product so unstable that they were unable to record meaningful physical constants.

As an alternate method of by-passing the reaction with pyridine hydrochloride, we struck upon the use of p-toluenesulfonic acid anhydride. The use of this reagent negated the possibility of replacement of the anomeric p-toluenesulfonate since the by-product in this case would

be the salt of p-toluenesulfonic acid and pyridine.


CH2OAc
AcO
O
AcO
HO
OH
+
TsOTs
Pyridine
CH2OAc
AcO
O
AcO
TsO
OTs
+
pyridine.HOTs

XXXII

XXXIV

The anhydride was readily prepared (70) and, after recrystallization, was remarkably stable. Two practical advantages of this material as compared to the acid chloride were immediately obvious. The compound was much less sensitive to aqueous hyrolysis, largely because it seemed completely insoluble in water, and further, it lacked the lingering strong odour of the chloride.

p-Toluenesulfonic acid anhydride was utilized in

reaction with 3,4,6-tri-O-acetyl-α-D-glucopyranose (XXXII) in the presence of pyridine. Since it was found that there was a strong evolution of heat during the addition of the anhydride, the reaction mixture was initially cooled. After about 20 hours at room temperature, a normal extractive work-up led to the isolation of an unstable syrup. Because of this instability, the material was utilized, in most cases, without further purification but one sample was subjected to buffered column chromatography and then employed for the observation of an n.m.r. spectrum (Fig. 18) as described in Table XI.

This n.m.r. spectrum corresponded exactly to expectations for tri-O-acetyl-1,2-di-O-p-toluenesulfonyl-α-D-glucopyranose (XXXIV). The integration of the C-methyl signal was sufficient to account for two p-toluenesulfonyl groups per molecule. Again, one of the acetyl signals was shifted upfield because of its proximity to a p-toluenesulfonyl group (88). Finally, the anomeric doublet was shifted down-field through the inductive effect of the anomeric sulfonate. The coupling constants were very similar to those observed in the starting material indicating again an α-configuration and C1 conformation.

This compound (XXIV) was the key intermediate in the alternate synthetic route to tri-O-acetyl-1,2-dideoxy-D-arabino-hex-1-enopyranose (I). The final step was an

TABLE XI

N.m.r. parameters (60 MHz) of tri-O-acetyl-1,2-di-O-p-toluenesulfonyl-α-D-glucopyranose (XXXIV) in deuteriochloroform.

Chemical shifts, τ value

H_1	H_2	H_3	H_4
3.95	5.39	4.62	4.95

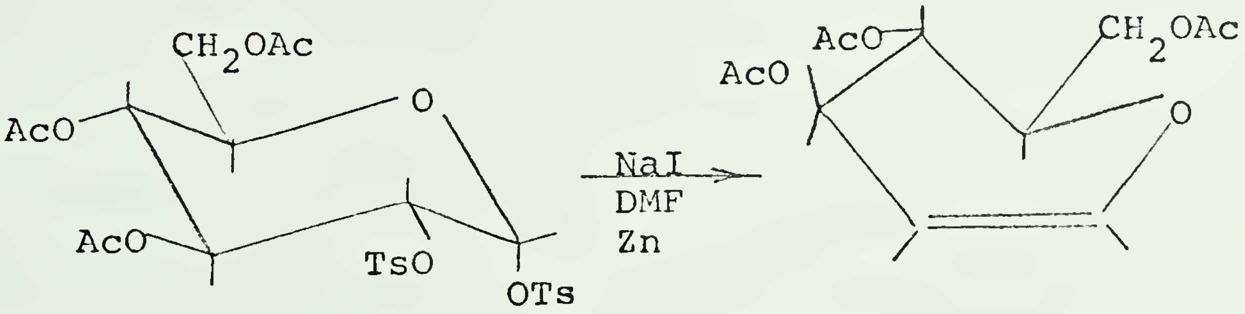
Chemical shifts, τ value

$H_{5,6,6'}$	C-methyl	Aromatic	Acetyl
5.7-6.2	7.55	2.0-2.7	7.95 8.03 8.21

Approximate coupling constants, Hz

$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
3.5	9.5	9.5	9.5

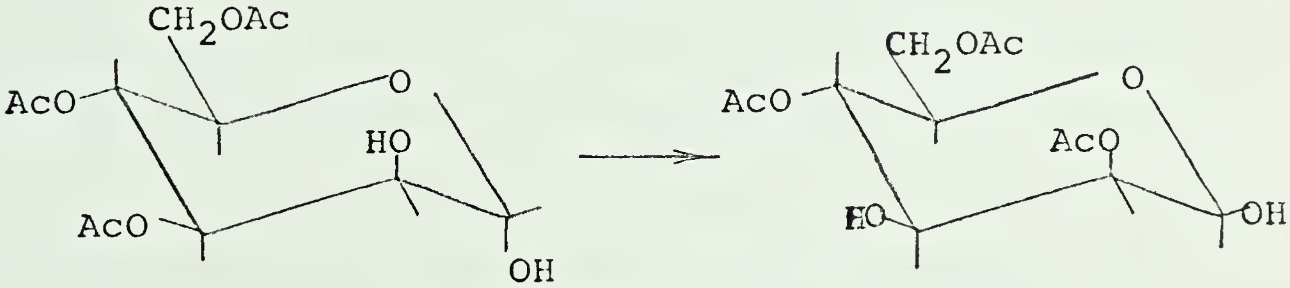
elimination reaction brought about under conditions described by Tipson and Cohen (53). Thus, the compound was treated with a 5% solution of sodium iodide in N,N-dimethylformamide. An excess of zinc dust was added to the mixture in order to remove the iodine by-product and thereby prevent its addition to the unsaturated sugar.



XXXIV I

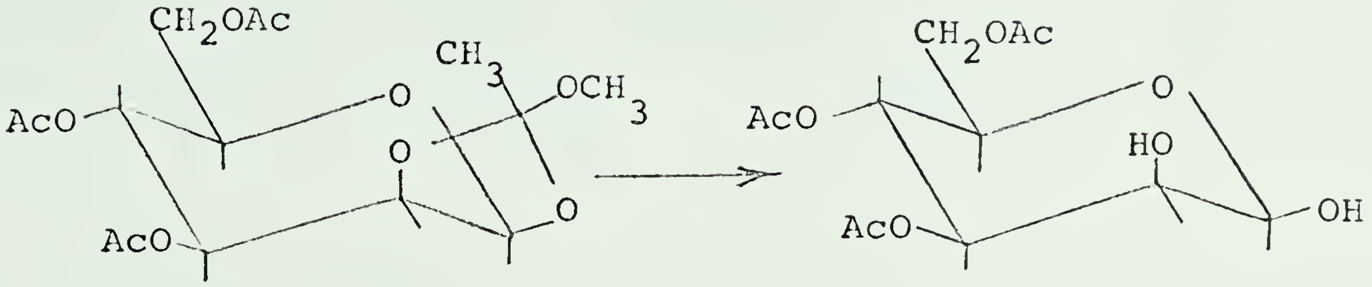
At a temperature of 105°, the reaction was complete in one and one half hours. After normal work-up, a clear syrup was isolated and the n.m.r. and i.r. spectra of this material co-incided exactly with those of an authentic sample of tri-O-acetyl-1,2-dideoxy-D-arabino-hex-1-enopyranose (I). The yield (74%) was sufficiently high to allow optimism concerning the possibility that this reaction might find some general applicability. Of course, in the ordinary synthesis of acetylated 1,2-unsaturated sugars, the previously described amalgam reduction was preferable since it involved only one step from the glycosyl bromide.

To further test the method, attention was turned to the mannopyranose configuration. Here again the first problem was to prepare the required 3,4,6-tri-O-acetyl-D-hexopyranose (XVIII). Initially, it was hoped to use the ethylene glycol orthoacetate equilibration method as previously described but small scale experiments indicated that this was effectively prevented by a rearrangement of the product which occurred under the reaction conditions.



XVIII LVIII

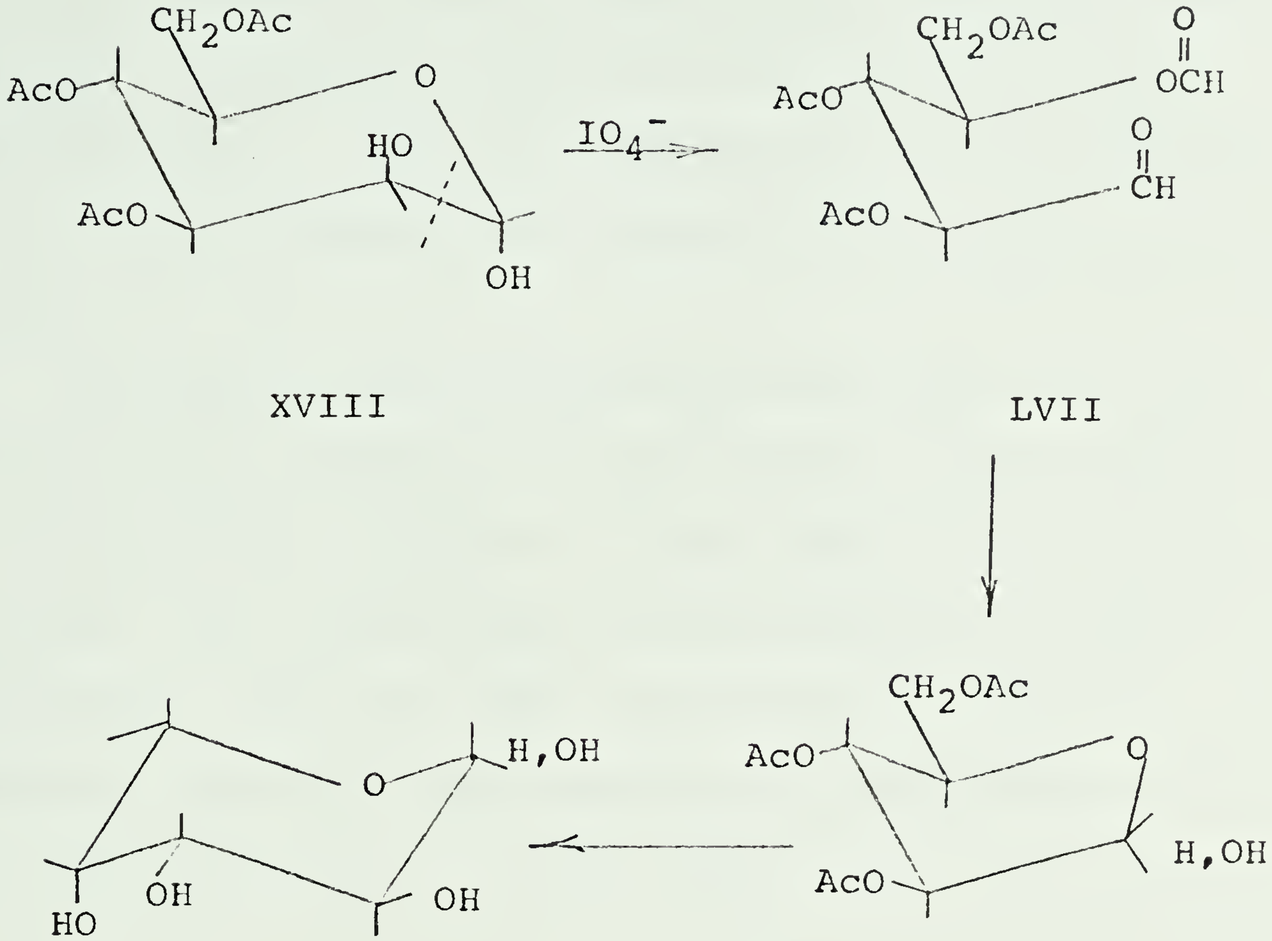
This rearrangement of 3,4,6-tri-O-acetyl-D-mannopyranose (XVIII) to 2,4,6-tri-O-acetyl-D-mannopyranose (LVIII) was reported by Perlin (65). He was able to isolate the 3,4,6-tri-O-acetate from a rapid equilibration of tri-O-acetyl-1,2-O-(1-methoxyethylidene)-β-D-mannopyranose in methanolic hydrogen chloride. Thus, this route was utilized here with some alteration.



XVII XVIII

The method was changed to include N,N-dimethylformamide as solvent and anhydrous p-toluenesulfonic acid as catalyst. A 12.5 M solution of methanol was sufficient to render the exchange rather complete in 7 minutes. A crystalline product was isolated in 72% yield.

Since the n.m.r. spectrum of 3,4,6-tri-O-acetyl-D-mannopyranose (XVIII) as reported by Perlin (65) and as observed here did not allow more than a rudimentary analysis, further proof of the structure of the product was obtained by a measured oxidation with sodium periodate. It was apparent from the results (Fig. 19) that each mole of (XVIII) consumed one and only one mole of periodate. The product of the oxidation was identified in a preparative oxidation reaction.


CH2OAc
AcO
AcO
O
HO
OH
IO4-
CH2OAc
AcO
AcO
O
OCH
O
CH
CH2OAc
AcO
AcO
O
H,OH
H,OH
O
OH
OH
HO

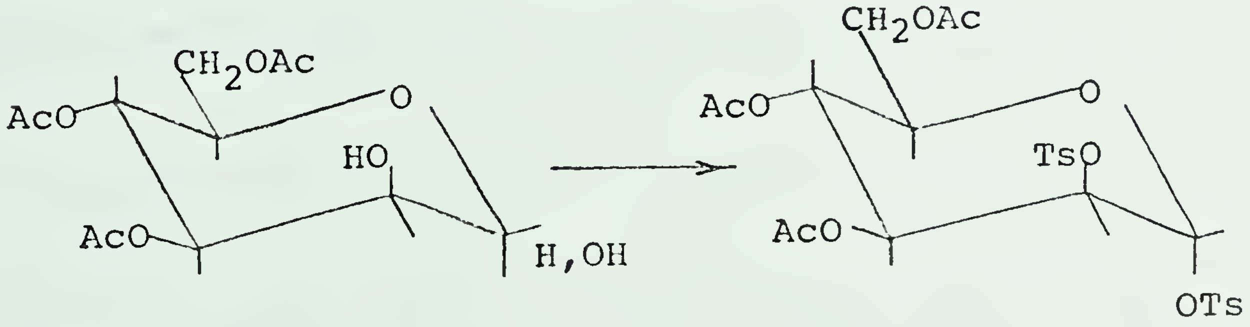
XVIII LVII

D-arabinose LIX

Two compounds were contained in the periodate oxidation mixture. A pure sample of one of these was separated by an extractive procedure. The n.m.r. spectrum of this sample contained two very low field signals which identified the compound as the initial oxidation product, 2,3,5-tri-O-acetyl-4-formyl-aldehydo-D-arabinose (LVII). The two low field signals were assigned to the "aldehyde" proton (τ 0.75) and the formate proton (τ 2.15). The

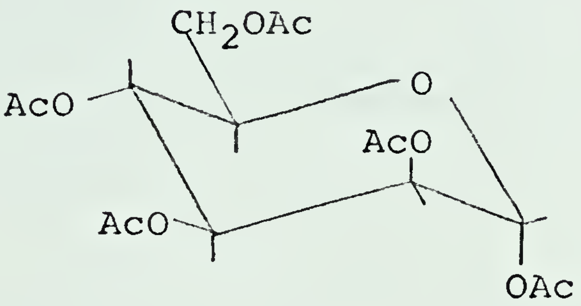
other compound in the mixture, while not available in a pure state, could be seen to lack these signals and was, therefore, assigned the structure, 2,3,5-tri-O-acetyl-D-arabinofuranose. After de-esterification, both compounds showed only the presence of D-arabinose on a paper chromatogram.

3,4,6-Tri-O-acetyl-D-mannopyranose (XVII) was converted to the 1,2-di-O-p-toluenesulfonyl compound (XXXV) in exactly the same fashion as described for the glucose compound. The instability of XXXV precluded stringent purification, but thin layer chromatographic methods indicated relatively high purity and a yield greater than 80%. The splitting of the low field doublet due to the anomeric proton in the n.m.r. spectrum indicated that the anomeric configuration was axial. The $J_{1,2}$ value (1.5 Hz) for this compound was comparable to that observed

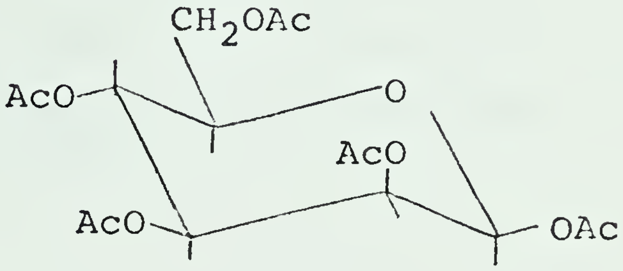


XVIII XXXV

in the spectrum of the α-penta-acetate (LX) ($J_{1,2}$ = 1.5 Hz) and somewhat larger than that shown in the spectrum of the β-penta-acetate (LXI) ($J_{1,2}$ = 1.1).

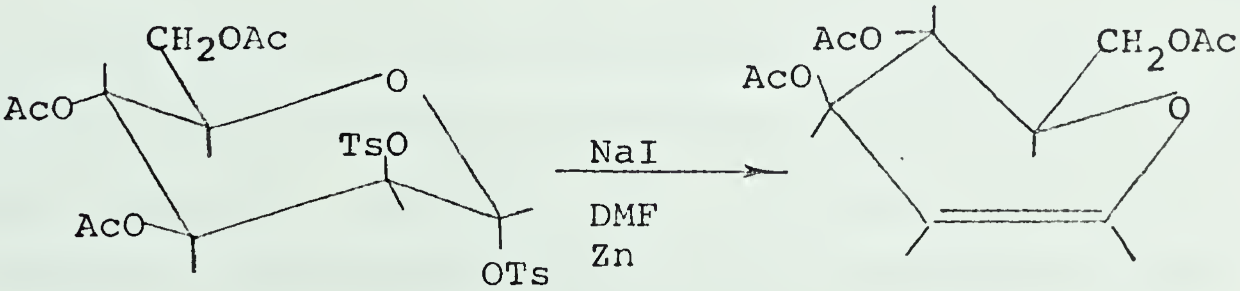

CH2OAc
AcO
O
AcO
AcO
OAc

LX


CH2OAc
AcO
O
AcO
AcO
OAc

LXI

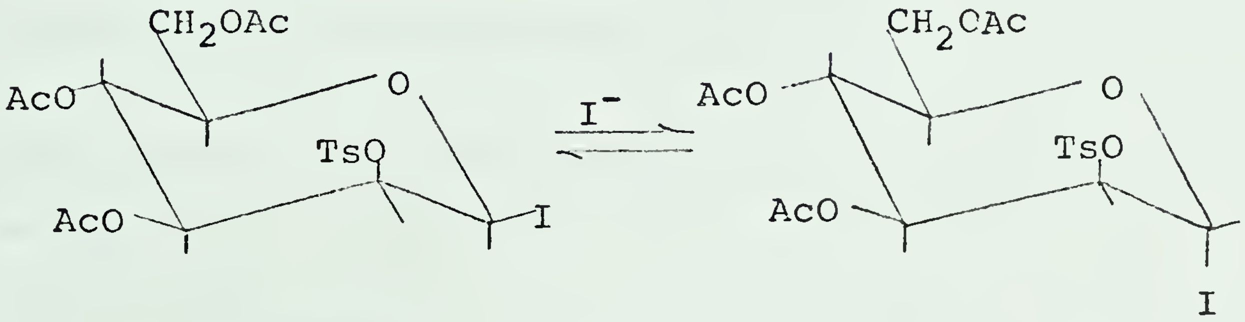
The last step in the synthesis of tri-O-acetyl-1,2-dideoxy-D-arabino-hex-1-enopyranose (I) from the manno configuration consisted of the treatment of the di-p-toluenesulfonate (XXXV) with sodium iodide and zinc dust.


CH2OAc
AcO
O
TsO
AcO
OTs
NaI
DMF
Zn
AcO
AcO
CH2OAc
O

XXXV

I

The desired product was obtained in somewhat reduced yield (53%) as compared to that observed in the *gluco* configuration. The synthesis did prove that the method was applicable both to the *cis* and to the *trans* 1,2-di-O-*p*-toluenesulfonyl derivatives of the hexopyranose structure. This was not surprising since the intermediate iodo-*p*-toluenesulfonate was expected to rapidly equilibrate in the presence of iodide ion. The *trans* isomer would then



be progressively removed in formation of the 1,2-unsaturated sugar.

An extension of the di-*p*-toluenesulfonate method to the disaccharide series was made through the use of maltose compounds. Synthesis of a 1,2-"diol" (3,6,2',3', 4',6'-hexa-O-acetylmaltose (XXXVIII)) was achieved by the glycol orthoacetate exchange route. The monomeric (XXXVI) and *bis*- (XXXVII) glycol orthoacetates of maltose

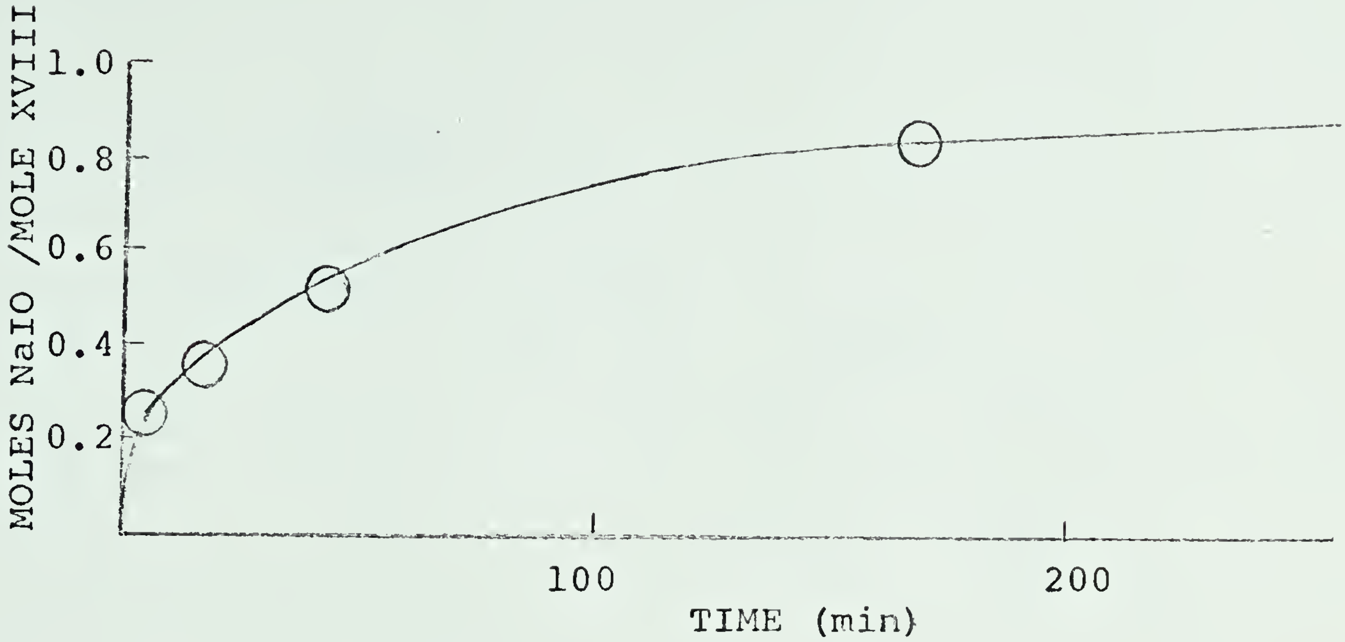


FIG. 19. Plot of sodium periodate oxidation of 3,4,6-tri-O-acetyl-D-mannopyranose (XVIII)

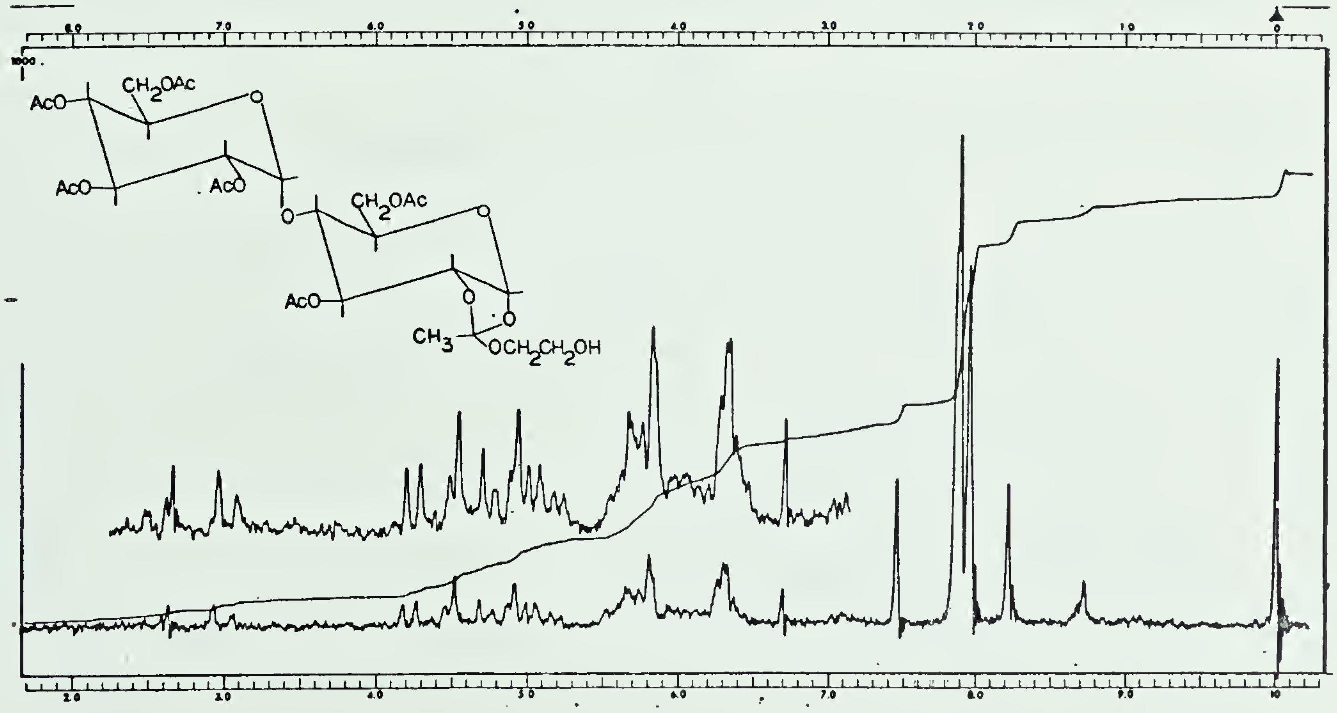
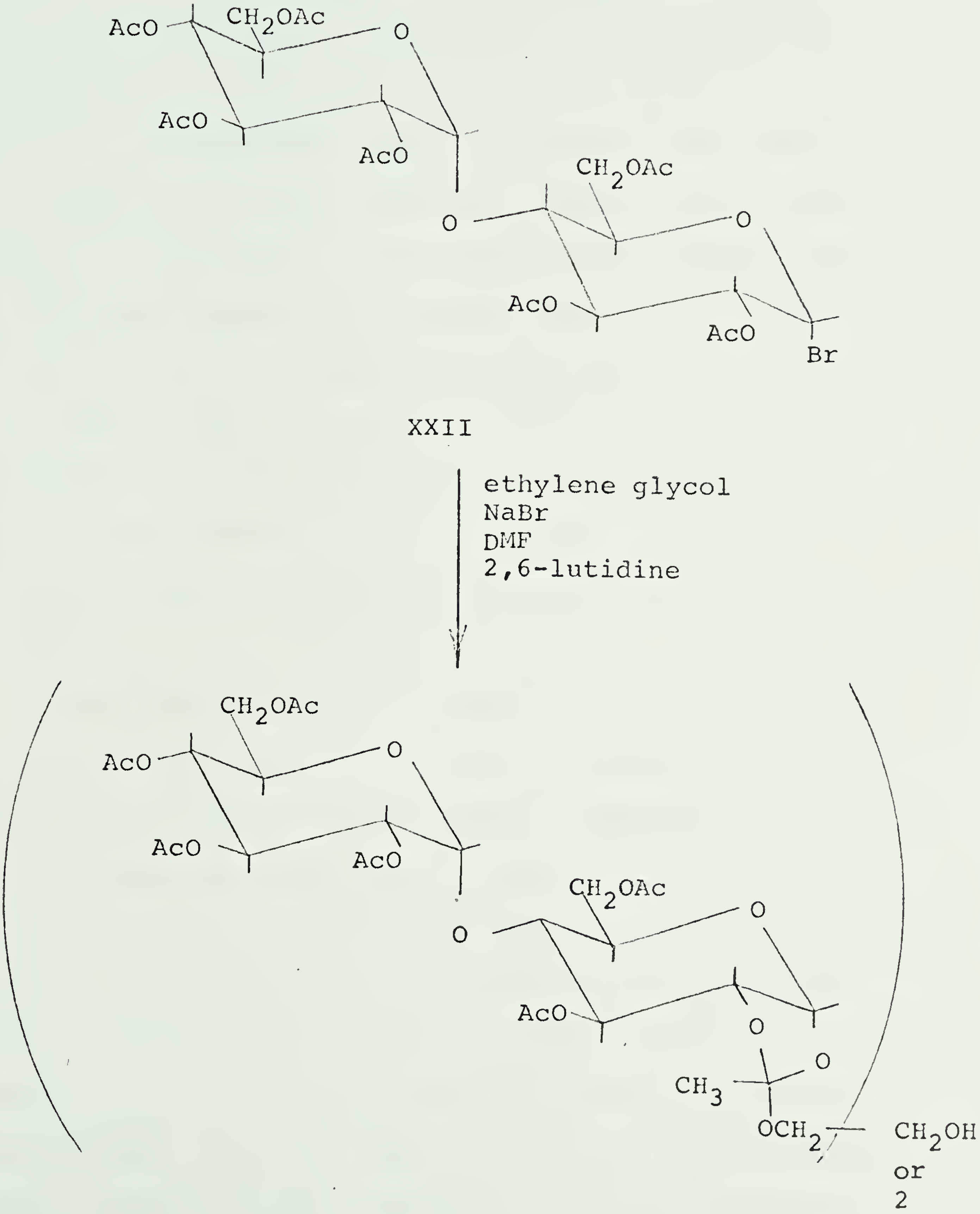
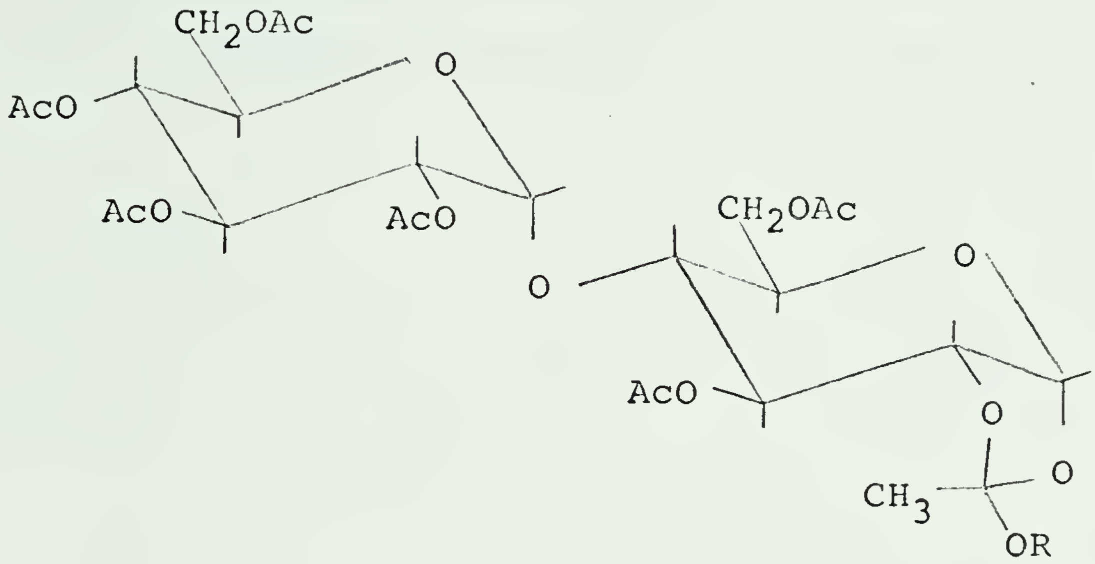


FIG. 20. N.m.r. spectrum (60 MHz) of 3,6-di-O-acetyl-4-O-(tetra-O-acetyl-α-D-glucopyranosyl)-1,2-O-(1-exo-2'-hydroxyethoxyethylidene)-α-D-glucopyranose (XXXVI) (deuteriochloroform)


AcO
CH$_2$OAc
O
AcO
AcO
O
CH$_2$OAc
O
AcO
AcO
Br
XXII
ethylene glycol
NaBr
DMF
2,6-lutidine
CH$_2$OAc
AcO
O
AcO
AcO
O
CH$_2$OAc
O
AcO
O
O
CH$_3$
OCH$_2$
CH$_2$OH
or
2

were prepared by treatment of hepta-O-acetyl-α-maltosyl bromide (XXII) with glycol in the presence of bromide ion and an acid scavenger. Separation of the products was achieved on a silicic acid column with a buffered eluant and by far the greatest amount of material was obtained as the bis-modification (XXXVII). Crystalline monomer (XXXVI) was isolated in 17% yield and was readily purified by recrystallization. The crystalline dimer unfortunately was found to be too labile for this latter procedure. In fact, every attempt at recrystallization of XXXVII led to recovery of XXXVI. Because of the large molecular weight of the XXXVII only the slightest traces of hydroxylic compounds would be necessary for this transformation.

As expected, the n.m.r. spectra of XXXVI (Fig. 20) and XXXVII were very similar and rather more complicated than those of similar monosaccharide compounds. They did show the anomeric signal in the normal position (τ 4.22) for such compounds and the splitting of the anomeric doublet (5.5 Hz) was exactly that shown by the corresponding glycol orthoacetates of glucose. These figures were comparable also to the values reported by Paulsen and coworkers (108) for their hexa-O-acetyl-1,2-O-(1-ethoxyethylidene)-α-maltose (LXII) prepared during the course of this work. No spectroscopic data was available for the other orthoacetyl derivative of maltose also reported during



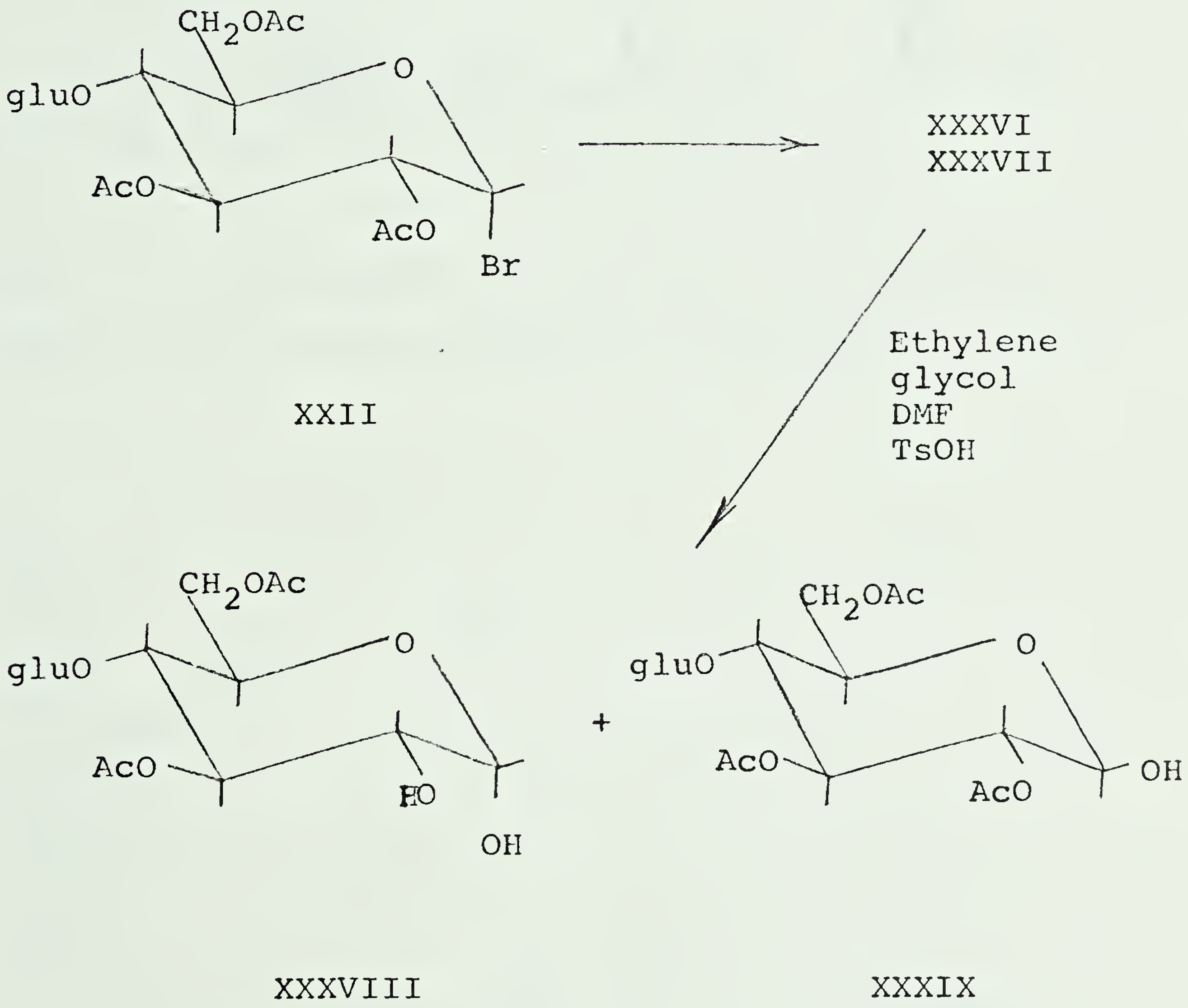
R = C_2H_5 (LXII)

= CH_3 (LXIII)

the course of this work. Kochetov and co-workers (109) utilized hexa-O-acetyl-1,2-O-(1-methoxyethylidene)-α-maltose (LXIII) for the preparation of a trisaccharide.

The equilibration reaction to produce the 3,6,2',3',4',6'-hexa-O-acetylmaltose (XXXVIII) was carried out in an "overall" fashion from the maltosyl bromide (XXII). That is to say, the glycol orthoacetates of maltose were produced and without isolation, were equilibrated with

an excess of ethylene glycol. Two products were found in the mixture obtained after removal of the catalyst and solvents. These were identified as the hexa-O-acetate (XXXVIII) (57% yield) and 2,3,6,2',3',4',6'- hepta-O-acetyl-β-maltose (XXXIX) (28% yield). The latter compound


CH2OAc
gluO
O
AcO
AcO
Br
XXII
XXXVI
XXXVII
Ethylene
glycol
DMF
TsOH
CH2OAc
gluO
O
AcO
HO
OH
+
CH2OAc
gluO
O
AcO
AcO
OH
XXXVIII
XXXIX

would be formed by hydrolysis reactions of orthoacetate compounds or the starting material (XXII).

The n.m.r. spectrum of the hexa-O-acetate XXXVIII unfortunately was not amenable to analysis and indeed did

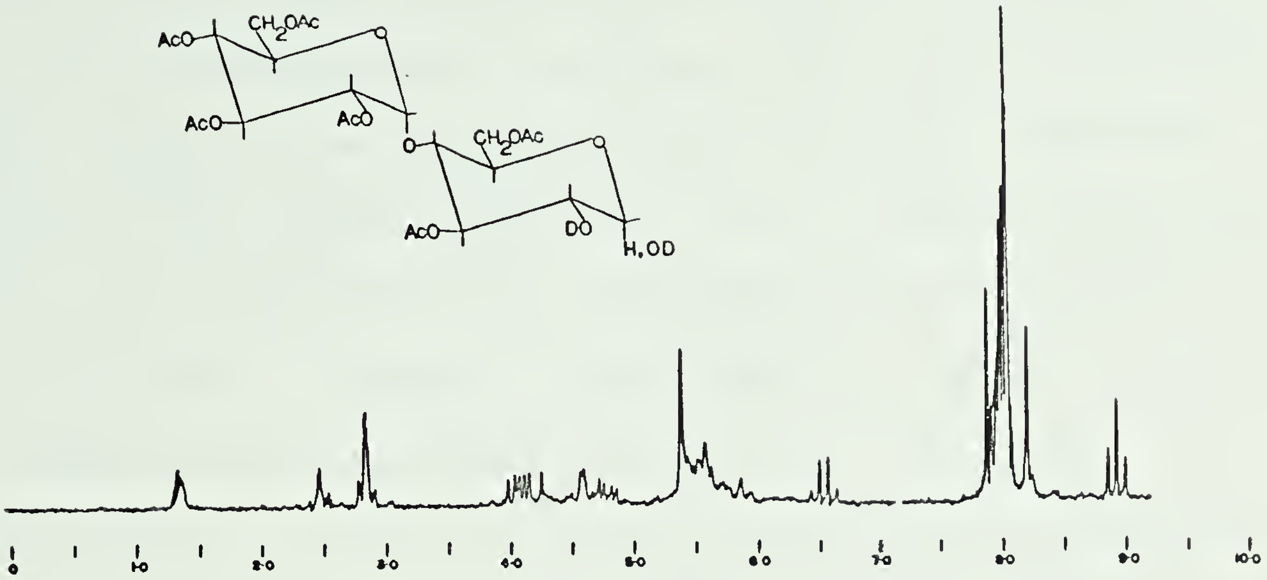


FIG. 21. N.m.r. spectrum (100 MHz) of 3,6,2',3',4',6'-hexa-O-acetyl-maltose (XXXVIII) (deuteriochloroform)

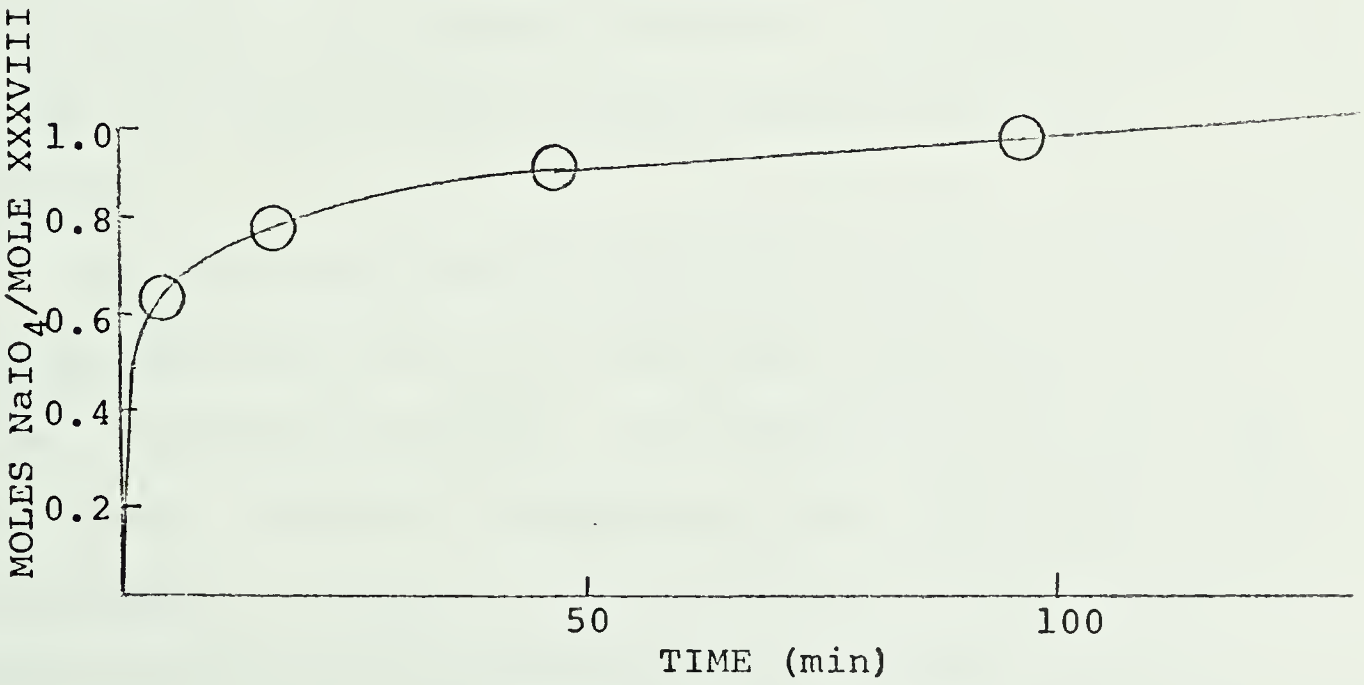
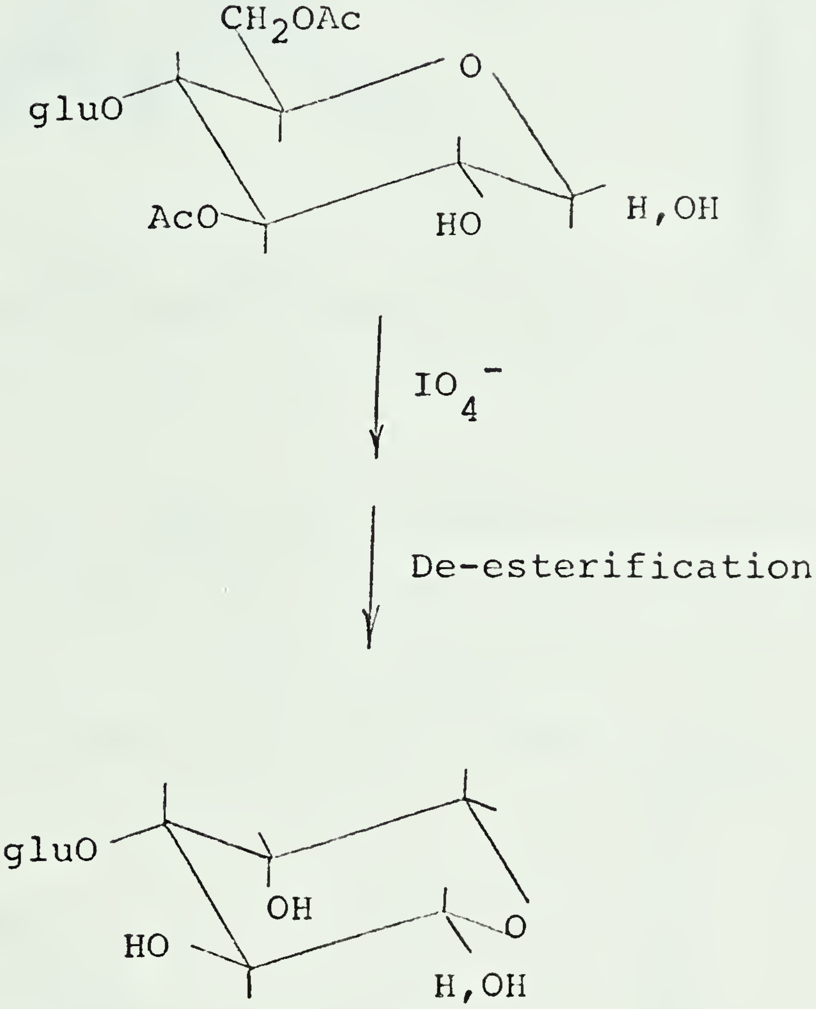


FIG. 22. Plot of sodium periodate oxidation of 3,6,2',3',4',6'-hexa-O-acetylmaltose (XXXVIII)

not allow the assignment of the anomeric configuration. It did indicate that the crystalline product contained about 1/2 mole of ethanol per mole. The specific rotation of this compound was somewhat higher than that reported by Wolfrom and DeLederkremer (97) for the small sample of material they isolated from a mutarotation of the hepta-O-acetate XXXIX. However, these workers reported a m.p. much higher than that found in this work. In view of the oxidation results described below and the eventual conversion of the compound to the known unsaturated derivative, there seemed no doubt that the material obtained here was, in fact, the hexa-O-acetate (XXXVIII). It seemed most probable that the present material and the earlier material merely represented different crystalline modifications of 3,6,2',3',4',6'-hexa-O-acetyl-β-maltose (XXXVIII).

Proof of the gross structure but not of the anomeric configuration was given by a measured oxidation with an excess of sodium periodate. As indicated in Fig. 22, the hexa-acetate (XXXVIII) consumed one mole and only one mole of periodate. A larger scale oxidation allowed identification of the de-acetylated oxidation product as 3-O-(α-D-glucopyranosyl)-D-arabinose (LXIV). This identification was achieved through chromatographic comparison with an authentic sample (96).

XXXVIII


CH2OAc
gluO
O
AcO
HO
H,OH
IO4−
De-esterification
gluO
OH
HO
O
H,OH

LXIV

Further proof of the structure of this oxidation product was available through hydrolysis of the glycosidic linkage. Both glucose and arabinose were chromatographically identified in the hydrolysate.

The synthetic sequence leading to a 1,2-unsaturated maltose was continued by the preparation of hexa-O-acetyl-1,2-di-O-p-toluenesulfonyl-α-maltose (XL).

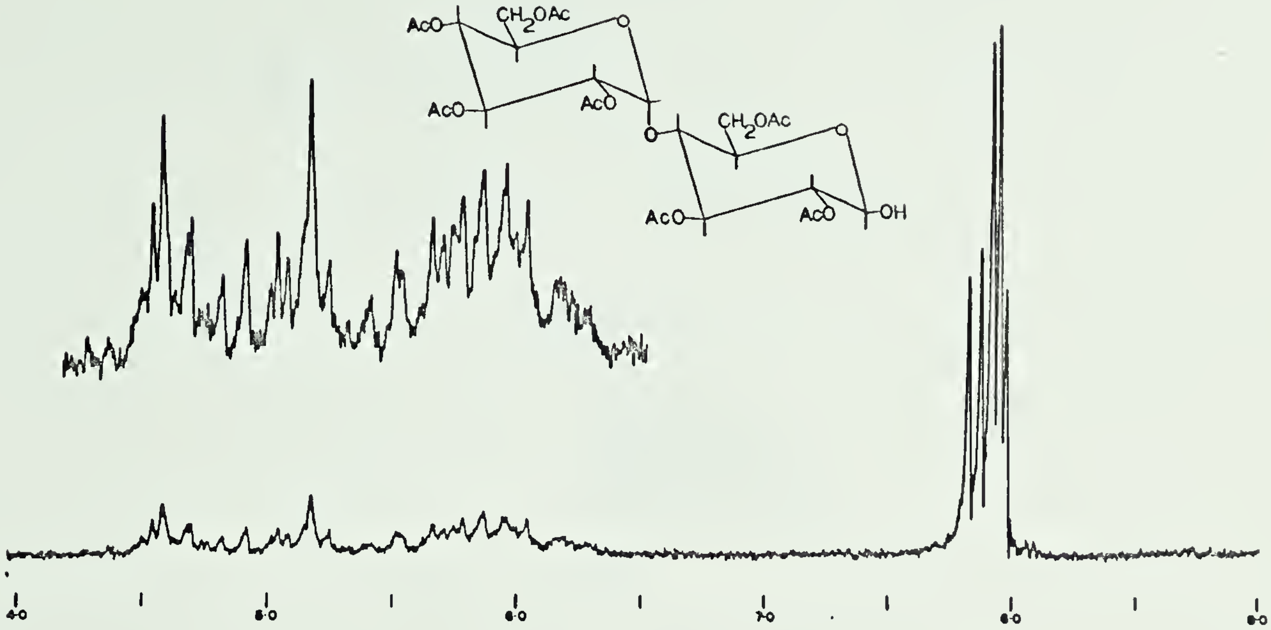


FIG. 23. N.m.r. spectrum (100 MHz) of 2,3,6,2',3',4',6'-hepta-O-acetyl-β-maltose (XXXIX) (deuteriochloroform)

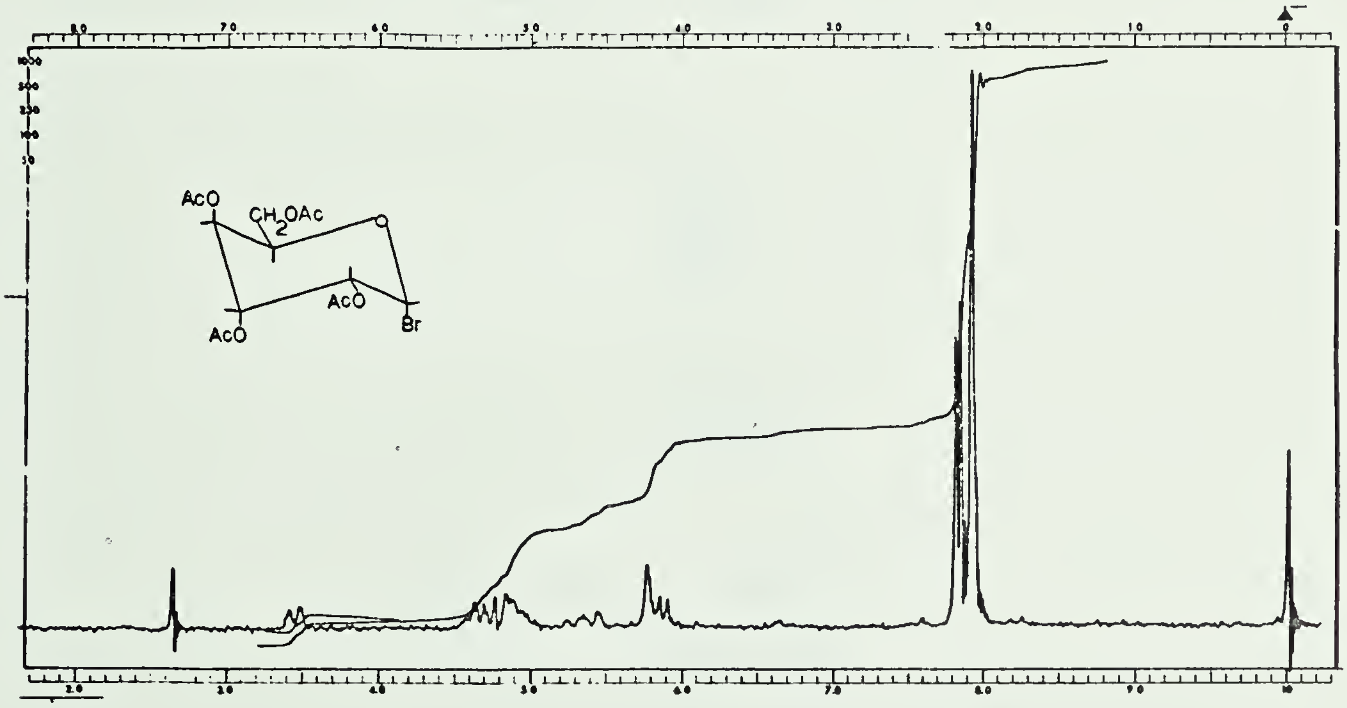
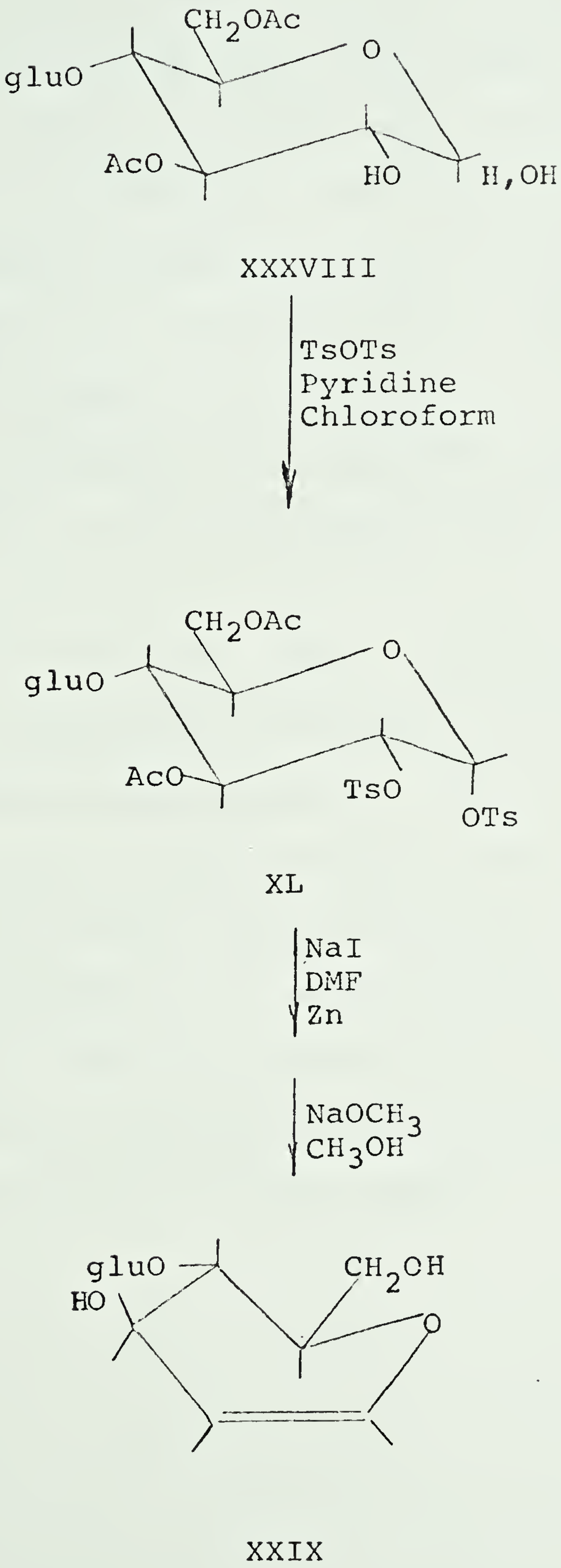


FIG. 24. N.m.r. spectrum (60 MHz) of tetra-O-acetyl-α-D-gulopyranosyl bromide (XLI) (deuteriochloroform)


CH_2OAc
O
gluO
AcO
HO
H,OH
XXXVIII
TsOTs
Pyridine
Chloroform
CH_2OAc
O
gluO
AcO
TsO
OTs
XL
NaI
DMF
Zn
$NaOCH_3$
CH_3OH
gluO
HO
CH_2OH
O
XXIX

The reaction was carried out in similar fashion to that in the gluco configuration but with an almost doubled reaction time. A rather unstable but chromatographically homogeneous syrup was obtained. The n.m.r. spectrum of the material, while cluttered, did show a distinct anomeric doublet at τ 3.99 with a splitting of 3.9 Hz. This latter value allowed assignment of the α-anomeric configuration. Because of its instability, this material was utilized in the preparation of the unsaturated sugar with no further purification.

As in the two previous cases, the di-p-toluenesulfonate (XL) was treated with a solution of sodium iodide in anhydrous N,N-dimethylformamide. Added zinc dust prevented the formation of the di-iodide of the unsaturated sugar. The crude product was de-acetylated before purification. 1,2-Dideoxy-4-O-(α-D-glucopyranosyl)-D-arabino-hex-1-enopyranose (XXIX) was obtained in a yield of 64.5% based on XL and was identified chromatographically by comparison to previously prepared samples.

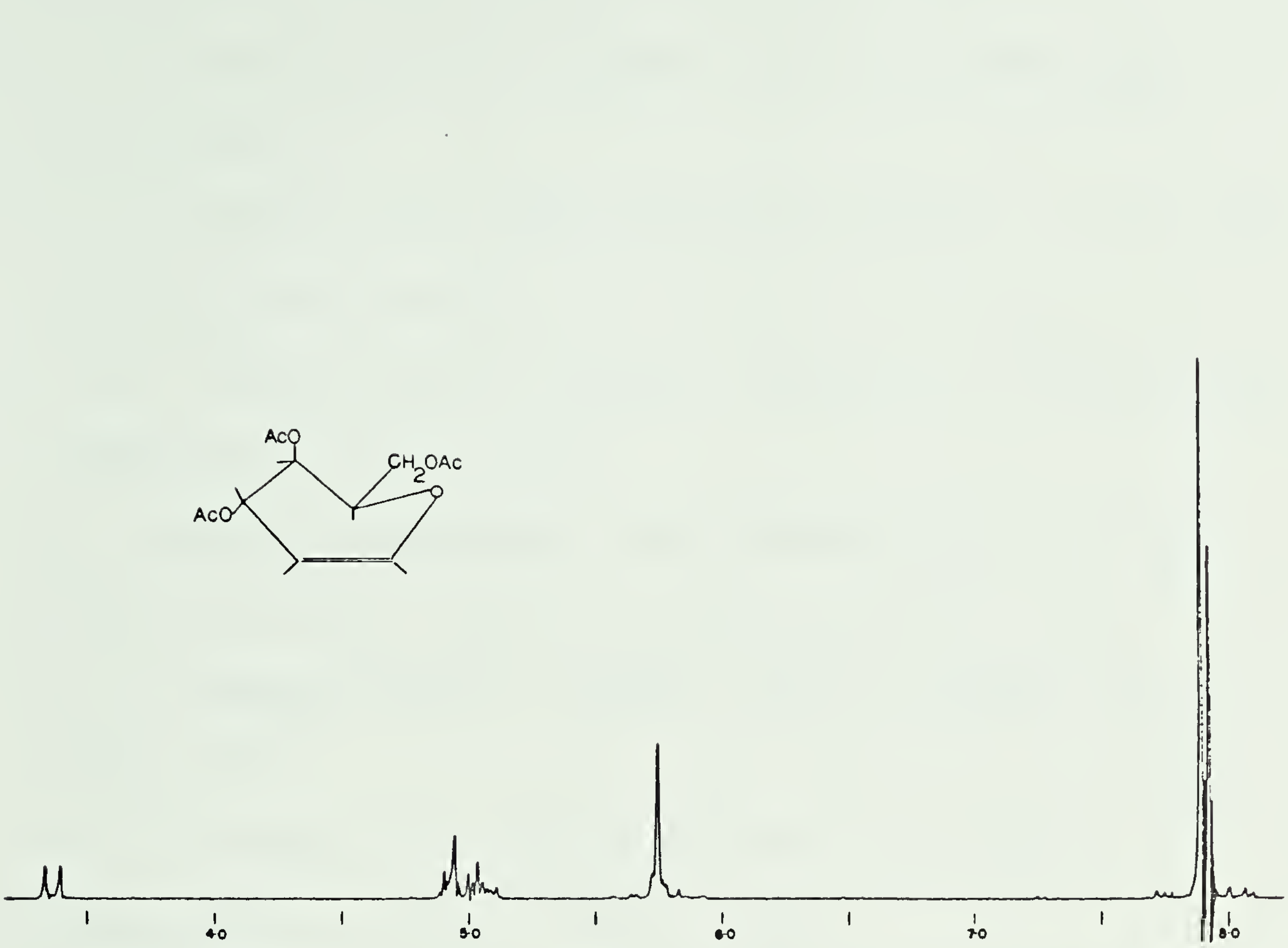


FIG. 25. N.m.r. spectrum (100 MHz) of tri-O-acetyl-1,2-dideoxy-D-xylo-hex-1-enopyranose (V) (deuteriochloroform)

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